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1. Frost, L. H., and Jackson, R. L.: J. Pediat. 39: 585-592, 1951.

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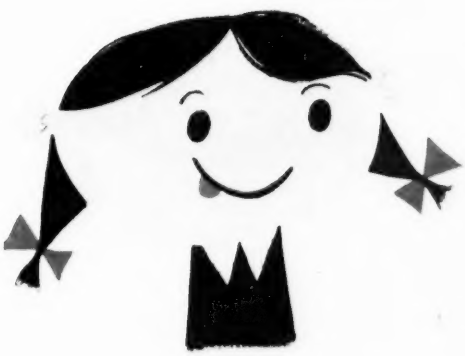

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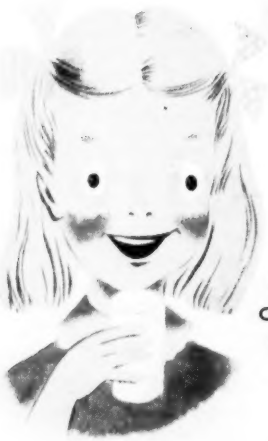

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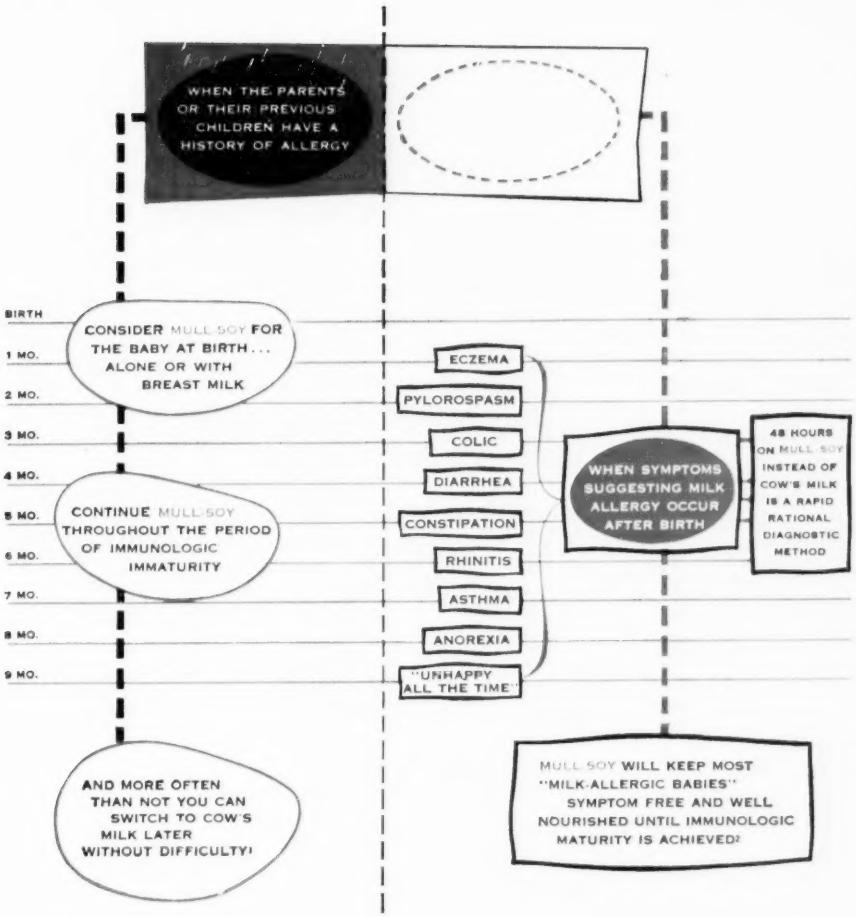
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1. Glaser, J., and Johnstone, D. E.: Ann. Allergy 10:433, 1952.
2. Clein, N. W.: Ann. Allergy 9:195, 1951.

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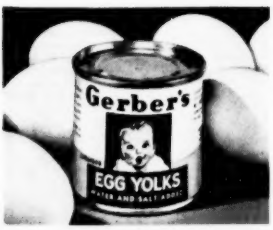

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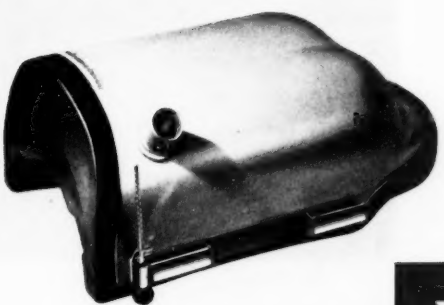

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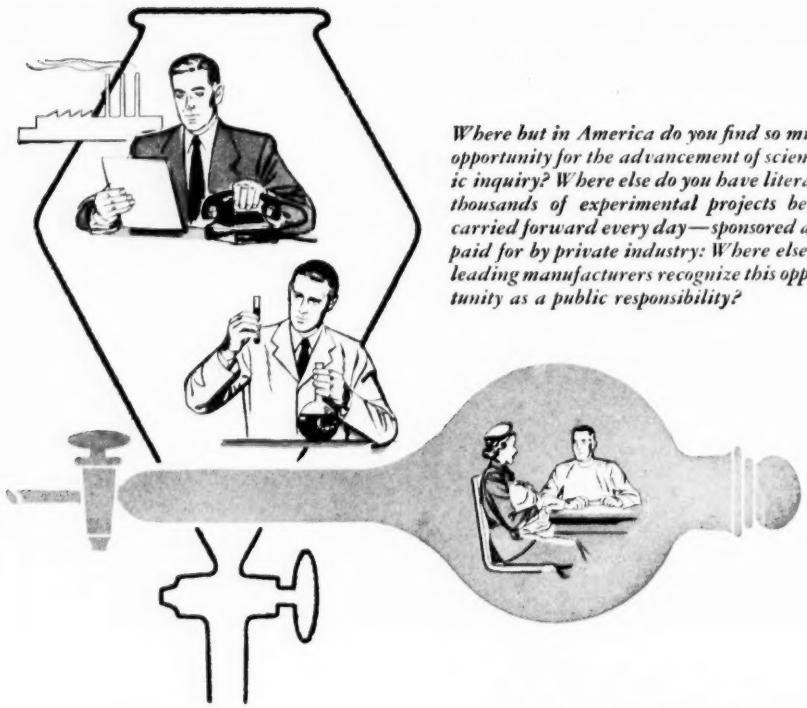

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American Journal of Diseases of Children

VOLUME 86 NOVEMBER 1953 NUMBER 5

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USE OF FERRIC AND FERROUS IRON IN THE PREVENTION OF HYPOCHROMIC ANEMIA IN INFANTS

W. L. NICCUM, M.D.
R. L. JACKSON, M.D.
AND
GENEVIEVE STEARNS, Ph.D.
IOWA CITY, IOWA

THE INCIDENCE of deficiency disease in infants has decreased concurrently with increase and dissemination of nutritional knowledge. However, hypochromic anemia continues to occur commonly in the latter half of the first year of life. It is desirable, therefore, to prevent rather than treat hypochromic anemia. This study was undertaken to determine the amount and form of iron needed for this purpose.

Since the studies of Elvehjem and co-workers,[1] Stearns and co-workers,[2] Heath and Patek,[3] and McClean,[4] iron preparations have been employed more frequently during the early months of postnatal life to prevent depletion of iron stores and to insure the availability of sufficient iron to maintain optimum hemoglobin values during infancy. Various amounts and types of iron have been advised as a daily dose. McClean [4] recommends 50 to 60 mg. of iron daily as ferrous sulfate; Elvehjem, 25 mg. of iron daily as ferric pyrophosphate and 1 mg. of copper daily as copper sulfate, and Stearns,[5] 5 to 10 mg. of iron daily as ferric ammonium citrate. In recent months excellent reports [6] of iron metabolism in normal, premature, and ill infants and children have been published which adequately review the literature and discuss the diagnosis and treatment of hypochromic anemia.

This study was supported by a grant from Mead Johnson & Company.

From the Department of Pediatrics, State University of Iowa College of Medicine.

1. (*a*) Elvehjem, C. A.; Peterson, W. H., and Mendenhall, D. R.: Hemoglobin Content of the Blood of Infants, Am. J. Dis. Child. **46**:105, 1933. (*b*) Elvehjem, C. A.; Siemers, A., and Mendenhall, D. R.: Effect of Iron and Copper Therapy on Hemoglobin Content of Blood of Infants, ibid. **50**:28, 1935.

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6. (*a*) Smith, C. H.; Schulman, I., and Morgenthau, J. E.: Iron Metabolism in Infants and Children, in Advances in Pediatrics, edited by S. Z. Levine and others, Chicago, Year Book Publishers, Inc., 1952, Vol. 5, p. 195. (*b*) Moore, C. V.: Iron Metabolism and Hypochromic Anemia, Currents in Infant Care, Nutrition, and Medicine, 1950, Vol. 2, p. 78.

The amount of iron available for the production of hemoglobin during early infancy is derived primarily from two sources. Iron is stored in the liver of the fetus during the latter half of the third trimester, and the amount is influenced considerably by the nutritional status of the mother.[7] Under optimum conditions, approximately 50 mg. of iron is stored in the fetal liver. Inasmuch as the amount of iron stored is related directly to the length of gestation, infants born prematurely or immaturely have less iron storage. Iron is made available after birth from the hemolysis of excess red blood cells. If it is assumed that the blood volume of a full-term infant at birth is approximately 450 ml., then an additional 150 to 180 mg. of iron would be made available for storage in this manner. There is very little loss of this iron, and it should be sufficient to aid in the production of another 300 to 450 ml. of whole blood.

It has been shown[8] that if the umbilical cord is not clamped until all pulsations cease approximately 100 ml. of blood will enter the infant's body which, during its breakdown, will make available approximately 45 mg. more iron for storage. This amount of iron may seem insignificant, but it approximates the amount of iron in the diet of many an infant during the first six months of extrauterine life. C. A. Smith and co-workers[9] have concluded, from their study of transplacentally acquired radioactive iron from maternal erythrocytes of healthy mothers, that the full-term infants whose cords were clamped late would have sufficient iron stored to prevent anemia for the first six months.

Guest[10] has observed that there is little likelihood of an iron-deficiency anemia developing in the first year of life in normal full-term infants without infection if an adequate amount of iron was provided during the intrauterine life. He believes an iron-deficiency anemia will not occur, even though the infant is fed a diet devoid of iron supplements. McCance and Widdowson,[11] basing their opinion on animal studies primarily and with the aid of mathematical determinations, have come to the conclusion that full-term infants have sufficient storage of iron to meet only 60% of their needs for the first six months after birth and that the other 40% might be obtained from human milk. This possibility seems doubtful, as mature human milk contains 0.07 to 0.36 mg. of iron per 100 ml.

Differences of opinion exist as to the relative efficiency of ferrous and ferric iron preparations in the prevention or treatment of iron-deficiency anemia. The investigations of Darby and Hahn,[12] in which they used radioactive ferrous chloride

7. Strauss, M. B.: Anemia of Infancy from Maternal Iron Deficiency in Pregnancy, J. Clin. Invest. **12**:345, 1933.

8. Wilson, E. E.; Windle, W. F., and Alt, H. L.: Deprivation of Placental Blood as a Cause of Iron Deficiency in Infants, Am. J. Dis. Child. **62**:320, 1941.

9. Smith, C. A.; Caton, W. L.; Roby, C. C.; Reid, D. E.; Caswell, R. S., and Gibson, J. G., II: Transplacental Iron: Its Persistence During Infancy as Studied Isotopically, Am. J. Dis. Child. **80**:856, 1950.

10. Guest, G. M.: Hypoferric Anemia in Infancy, in Symposium on Nutrition: Nutritional Anemia, Cincinnati, Robert Gould Research Foundation, Inc., 1947, p. 161.

11. McCance, R. A., and Widdowson, E. M.: The Metabolism of Iron During Suckling, J. Physiol. **112**:450, 1951.

12. (*a*) Darby, W. J.; Hahn, P. F.; Kaser, M. M.; Steincamp, R. C.; Densen, P. M., and Conk, M. B.: The Absorption of Radioactive Iron by Children 7 to 10 Years of Age, J. Nutrition **33**:107, 1947. (*b*) Hahn, P. F.; Carothers, E. L.; Cannon, R. O.; Sheppard, C. W.; Darby, W. J.; Kaser, M. M.; McClellan, G. S., and Densen, P. M.: Iron Uptake in 750 Cases of Human Pregnancy Using the Radioactive Isotope Fe^{59}, Fed. Proc. **6**:392, 1947.

(2 to 3 mg. of $FeCl_2$ containing Fe^{59}, 47-day half-life, reduced with a slight excess of ascorbic acid and given orally) indicated that ferrous iron is utilized more efficiently by the intestinal mucosal cells. This work corroborates the clinical observations of Moore [13] in earlier experiments. Stearns and Stinger,[26] in earlier studies, had observed that ferric iron, when given in small amounts in the form of ferric ammonium citrate, was retained and utilized well by healthy infants. Small amounts of ferric iron apparently are reduced to ferrous iron in the gastrointestinal tract. The utilization of iron from such foods as egg yolk and fortified cereals (the iron in egg yolk is 1.0 to 1.5 mg. ferrous iron in an organic form and in the fortified cereal, 8.5 mg. of ferrous iron per ounce) was also studied by the latter group of investigators. The total intake required to insure retention of iron was found to be 0.5 mg. per kilogram of body weight, and intakes up to 1.0 to 1.5 mg. per kilogram allowed ample retention for hemoglobin formation.

The gradient of absorption of iron is thought to be greater in the duodenum and upper ileum,[14] and excretion of iron by the gastrointestinal tract is probably a function of the colon.[15]

Granick has reviewed [16] the literature on absorption of iron which supports the conclusion that ferrous is more readily absorbed than ferric iron. He attempts, from his experimental data, to explain the exact role of ferritin in the regulation of absorption and excretion of iron. It is his opinion that the amount of iron in the ferrous state that is absorbed by the mucosal cell is regulated by a factor called the mucosal block, which in turn is related to the relative or absolute amount of ferrous iron contained in the cell and indirectly to the amount of ferritin contained therein. He further reports that the quantity of ferric iron being released from the cell to the blood stream is dependent on the relative "redox" level of that cell and observed this to be a function of the reduced oxygen tension in the blood stream. The fraction of the blood plasma protein transporting the iron is designated as siderophilin. Schade and Caroline [17] have isolated chemically a globulin fraction of plasma, which they believe aids in the transport of iron in the ferric state and is presumably the siderophilin described by Granick.

Human or cow's milk contains small and varying amounts of iron, with mean values reported respectively as 0.07 and 0.18 mg. per 100 ml.,[18] 0.010 and 0.50 mg.

13. Moore, C. V.; Dubach, R.; Minnich, V., and Roberts, H. K.: Absorption of Ferrous and Ferric Radioactive Iron by Human Subjects and by Dogs, J. Clin. Invest. **23**:755, 1944.

14. Footnote 13. McCance, R. A., and Widdowson, E. M.: Absorption and Excretion of Iron Following Oral and Intravenous Administration, J. Physiol. **94**:148, 1938. Hahn, P. F.; Jones, E.; Lowe, R. C.; Mencely, C. R., and Peacock, W.: The Relative Absorption and Utilization of Ferrous and Ferric Iron in Anemia as Determined by Radioactive Isotope, Am. J. Physiol. **143**:191, 1945.

15. Hahn, P. F.; Bale, W. F.; Hettig, R. A.; Kamen, M. D., and Whipple, G. H.: Radioactive Iron and Its Excretion in Urine, Bile, and Feces, J. Exper. Med. **70**:443, 1939. Footnote 4.

16. (*a*) Granick, S.: Ferritin: Increase of Protein Apoferritin in the Gastrointestinal Mucosa as a Direct Response to Iron Feeding; The Function of Ferritin in the Regulation of Iron Absorption, J. Biol. Chem. **164**:737, 1946; (*b*) Structure and Physiological Functions of Ferritin, Physiol. Rev. **31**:489, 1951.

17. Schade, A. L., and Caroline, L.: An Iron-Binding Component in Human Blood Plasma, Science **104**:340, 1946.

18. Marriott, quoted by Brennemann, J.: Artificial Feeding of Infants, Brennemann's Practice of Pediatrics, Hagerstown, Md., W. F. Prior Company, Inc., 1948, Vol. I, Chap. 26.

per 100 ml.[19] and 0.36 and 0.13 mg. per 100 ml.[20] Supplemental foods commonly given during the first year of extrauterine life that contain appreciable amounts of iron are the following: egg yolk, 1 to 2 mg. per yolk as ferrous iron; pureed meats, 1 to 4 mg. per ounce as ferrous iron and fortified cereals, averaging 8.5 mg. as ferrous iron per ounce of dried cereals. Fruits and vegetables which contain appreciable amounts of iron [4] are the following: peaches, prunes, green beans, peas, sweet potatoes, and carrots. The form of iron in these foods is difficult to ascertain.

The average daily requirements of iron for the first year of life, recommended by the Food and Nutrition Board of the National Research Council, is 6 mg. per day.[21] The form of iron advised is not specified.

This study was undertaken to determine both the desirability of using iron prophylactically and the relative effectiveness of ferric and ferrous salts, by observing the hemoglobin response of full-term, immaturely born, and prematurely born infants receiving nutritionally adequate diets of known content, supplemented by small prophylactic doses of ferric or ferrous salts.

MATERIALS AND METHODS

Eighteen full-term infants were observed in the metabolism ward for 6- to 12-month periods, from June, 1949, until June, 1952. Two premature infants were observed in the metabolism ward during this period whose birth weights were 5 lb. 1 oz. (2,300 gm.) and 4 lb. 8 oz. (2,040 gm.). The records of 115 full-term infants who were in the metabolism ward for 6- to 12-month periods during the years 1939 to 1949 were reviewed. The records of a set of twins, whose birth weights were 6 lb. (2,720 gm.) each, and of a set of triplets, whose birth weights were 3 lb. 14 oz. (1,760 gm.), 3 lb. 10 oz. (1,640 gm.), and 3 lb. 11 oz. (1,670 gm.), were reviewed.

Nineteen full-term infants were observed in the well-baby clinic. Two premature infants also were observed in the well-baby clinic whose birth weights were 3 lb. 15 oz. (1,790 gm.) and 4 lb. 6½ oz. (2,000 gm.).

Ferric ammonium citrate was fed to all infants in the metabolism ward during the first 10 years of the study. The dose given was 5 mg. of iron daily at 3 months of age, increased to 10 mg. of iron daily after 6 months of age. All of the other infants observed in the metabolism ward and outclinic received a concentrated ferrous sulfate preparation [22] fed in exactly the same manner. All iron was given to the infants in their formulas.

The diets of all infants in the metabolism ward were weighed and measured, and aliquot specimens were examined chemically for other metabolic studies. Modified whole-milk feedings were given. During several of the periods, such feedings as protein hydrolysates, soybean formulas, and varying amounts of vitamin D were given these children. The infants observed in the well-baby clinic were from intelligent families of the higher socioeconomic groups. The diet schedule and other supplements given these infants are reported by one of us elsewhere.[23] All infants made satisfactory growth in height and weight, and all progressed normally in their neuromotor development.

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19. Jeans, P. C., and Marriott, W. Mc.: Infant Nutrition: A Textbook of Infant Feeding for Students and Practitioners of Medicine, Ed. 4, St. Louis, C. V. Mosby Company, 1947, p. 158.

20. Macy, I. G.; Kelley, H., and Sloan, R.: The Composition of Milks: A Compilation of the Comparative Composition and Properties of Human, Cow, and Goat Milk, Colostrum, and Transitional Milk, Bulletin of the National Research Council, No. 119, 1950, p. 23.

21. Food and Nutrition Board, National Research Council: Recommended Dietary Allowances, Revised 1948, Reprint and Circular Series No. 129, 1948, p. 16.

22. Solution containing 125 mg. ferrous sulfate or 25 mg. of ferrous iron per cubic centimeter labeled Fer-In-Sol, supplied by Mead Johnson & Company.

23. Jackson, R. L.: College of Medicine Symposium on Infant Feeding: Feeding of Healthy Infants, J. Iowa M. Soc. **40**:159, 1950.

Some of the infants observed in the metabolism ward acquired upper respiratory infections of varying degrees of severity and duration. Prior to the availability of antibacterial agents, more severe and prolonged infections occurred. Mild upper respiratory infections also occurred in some of the infants observed in the well-baby clinic.

The hemoglobin values of infants with respiratory infections are tabulated separately. The infections were classed as severe if a complication such as otitis media or pneumonitis developed or a prolonged low-grade infection was recorded. These severe or chronic infections usually began between the 20th and 25th weeks of life. All of these infants were in the group fed ferric ammonium citrate. Infections other than those noted above were slight; no infant had more than three mild infections with or without fever, often consisting only of a slight rhinitis.

TABLE 1.—*Data on Infants Fed Ferric Ammonium Citrate Who Were Observed in the Metabolism Ward with No Infection*

Age, Wk.	No. Determinations	Hemoglobin, Gm./100 Ml. (Mean)	Age, Wk.	No. Determinations	Hemoglobin, Gm./100 Ml. (Mean)
1	2	19.5	27	27	11.6
2	9	17.2	28	24	11.8
3	22	15.6	29	23	11.9
4	20	13.7	30	23	11.6
5	24	13.3	31	24	11.5
6	25	12.3	32	23	11.4
7	27	10.8	33	22	11.4
8	27	11.4	34	21	11.7
9	31	11.0	35	19	11.4
10	32	10.2	36	17	11.5
11	34	10.9	37	14	11.6
12	27	10.9	38	16	11.7
13	31	10.9	39	15	11.7
14	33	11.8	40	15	11.2
15	34	11.3	41	12	11.3
16	35	11.3	42	11	11.5
17	33	11.6	43	11	11.2
18	36	11.4	44	10	11.2
19	36	11.8	45	7	10.8
20	34	11.6	46	6	11.5
21	36	11.9	47	6	11.5
22	34	11.7	48	5	11.1
23	32	11.9	49	5	11.3
24	30	11.8	50	5	11.2
25	28	11.4	51	1	11.3
26	29	11.7	52	1	11.8

All infants in the metabolism ward were subjects of other metabolic studies and because of this were having repeated venipunctures. During the early part of the study, when vitamin D requirement was studied, approximately 10 to 15 ml. of blood was drawn every four to six weeks. After 1949, only 5 to 10 ml. of blood was withdrawn from each infant every four to six weeks. It was calculated that the total amount of serum iron withdrawn from these infants during the period of this study amounted to approximately 15 to 16 mg., which would not result in significant difference in the hemoglobin values of the two groups of infants.

Hemoglobin determinations were made by the Newcomer method,[24] with a visual colorimeter up to 1945, and a Klett-Summerson photoelectric colorimeter after that time. The instruments are standardized with oxyhemoglobin and carbon monoxide hemoglobin. Hemoglobin values were determined, for the most part, at weekly intervals on all infants in the metabolism ward, and at monthly intervals in the outpatient group.

The mean hemoglobin values with number of determinations and age in weeks of all infants are tabulated in Tables 1 to 5, inclusive. The mean hemoglobin values have been plotted and a

24. Newcomer, H. S.: Absorption Spectra of Acid Hematin, Oxyhemoglobin, and Carbon Monoxide Hemoglobin: A New Hemoglobinometer, J. Biol. Chem. **37**:465, 1919.

TABLE 2.—*Data on Infants Fed Ferric Ammonium Citrate Who Were Observed in the Metabolism Ward with Mild Infections*

Age, Wk.	No. Determinations	Hemoglobin, Gm. 100 Ml. (Mean)	Age, Wk.	No. Determinations	Hemoglobin, Gm. 100 Ml. (Mean)
1	2	19.5	26	31	11.7
2	11	17.3	27	30	11.5
3	23	16.2	28	31	11.7
4	23	14.5	29	29	11.8
5	24	13.5	30	30	11.6
6	27	12.4	31	25	11.9
7	24	11.2	32	23	11.9
8	24	11.5	33	25	11.5
9	28	11.0	34	24	11.8
10	30	11.0	35	21	11.9
11	28	10.9	36	17	11.7
12	34	11.1	37	17	11.2
13	33	11.3	38	16	11.8
14	36	11.1	39	13	12.2
15	40	11.3	40	13	12.3
16	38	11.3	41	12	12.5
17	35	11.3	42	11	11.8
18	37	11.4	43	10	11.7
19	32	11.4	44	9	11.8
20	36	11.4	45	8	11.6
21	38	11.9	46	7	12.0
22	35	11.5	47	7	11.2
23	34	11.4	48	4	11.7
24	33	11.5	49	3	12.4
25	36	11.8	50	3	12.3
			51	2	11.6

TABLE 3.—*Data on Infants Fed Ferric Ammonium Citrate Who Were Observed in the Metabolism Ward with Severe Infections*

Age, Wk.	No. Determinations	Hemoglobin, Gm. 100 Ml. (Mean)	Age, Wk.	No. Determinations	Hemoglobin, Gm. 100 Ml. (Mean)
1	..	....	25	13	11.5
2	3	17.5	26	15	11.3
3	7	17.4	27	14	11.3
4	9	15.4	28	14	11.0
5	12	13.0	29	17	11.7
6	12	11.6	30	11	11.3
7	12	11.1	31	12	11.5
8	12	10.8	32	11	11.9
9	12	10.9	33	9	11.3
10	14	10.7	34	9	11.0
11	14	10.3	35	9	10.8
12	13	10.8	36	8	10.9
13	14	11.5	37	9	10.5
14	13	11.3	38	9	10.6
15	12	10.8	39	8	10.7
16	12	11.2	40	7	11.3
17	12	11.0	41	7	11.2
18	12	11.0	42	7	10.8
19	12	11.6	43	7	11.3
20	13	11.4	44	7	10.8
21	14	12.1	45	6	11.0
22	13	11.6	46	3	10.8
23	13	11.7	47	2	11.6
24	14	11.3	48	3	11.2

smoothed mean curve drawn to demonstrate the values obtained (Charts 1 and 2). The two groups of published data [25] to which our data are compared are so labeled where they appear. A scatter pattern of the values obtained for the metabolism-ward infants who received ferrous salts is shown in Chart 3.

TABLE 4.—*Data on Infants Fed Ferrous Sulfate Who Were Observed in the Metabolism Ward*

Age, Wk.	No. Determinations	Hemoglobin, Gm. 100 Ml. (Mean)	Age, Wk.	No. Determinations	Hemoglobin, Gm. 100 Ml. (Mean)
1	7	16.2	28	6	12.5
2	7	13.4	29	5	12.7
3	7	13.4	30	5	12.5
4	7	12.6	31	6	12.5
5	8	11.2	32	5	13.1
6	6	11.7	33	5	13.2
7	8	11.1	34	4	12.1
8	8	10.2	35	4	13.5
9	10	11.2	36	5	13.2
10	8	10.6	37	5	13.2
11	9	11.0	38	7	13.0
12	8	11.4	39	4	13.0
13	.	11.4	40	3	13.2
14	9	11.4	41	3	12.6
15	7	11.6	42	3	12.5
16	7	11.7	43	4	12.8
17	9	11.2	44	3	12.7
18	9	12.2	45	4	11.8
19	5	12.0	46	4	13.0
20	5	12.2	47	3	12.7
21	11	12.7	48	2	12.4
22	6	12.3	49	2	12.8
23	8	12.6	50	1	11.2
24	8	12.6	51	3	12.4
25	9	12.5	52	1	12.6
26	8	12.1	53	1	11.2
27	7	13.0	54	1	12.4

TABLE 5.—*Data on Infants Fed Ferrous Sulfate Who Were Observed in the Well-Baby Clinic*

Age, Mo.	No. Determinations	Hemoglobin, Gm. 100 Ml. (Mean)
2	9	12.0
3	3	10.3
4	15	11.6
5	7	12.1
6	7	12.0
7	3	11.9
8	3	11.9

Representative standard deviations have been calculated on our data at 29 weeks and 38 weeks for all the infants in the metabolism ward in order to make comparisons between our data and those reported by other investigators. The group of infants seen in the well-baby clinic was small, and the number of values did not lend itself to statistical analysis.

In late infancy, the number of hemoglobin values for each week was too small to give reliable means for certain of the groups studied. As mean hemoglobin values for adjacent weeks were nearly identical, the data for two to three weeks have been combined (Table 6).

25. Footnotes 1 and 16b.

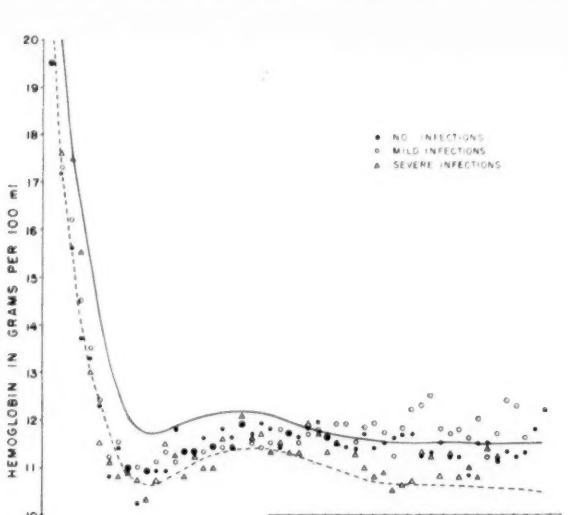

Chart 1.—Mean hemoglobin determinations of all infants receiving ferric ammonium citrate in the dosage shown. The solid line represents the mean values reported by Elvehjem and the broken line the mean values reported by Kato. Comparison is made between patients with and without infection and the severity of infection.

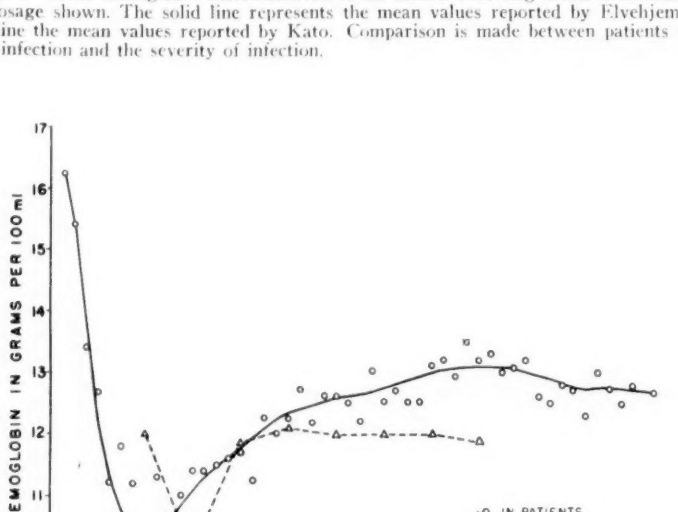

Chart 2.—Mean hemoglobin values of all infants fed ferrous sulfate in the dosage shown. Refer to Chart 1 for mean values reported by others.

The formulas used for determining standard deviation, standard error of the mean, and "significant ratio t" are those in common usage.[26]

RESULTS

A total of 2,804 hemoglobin determinations were made on the blood of 115 infants who were fed ferric ammonium citrate from the 12th to the 52d weeks of life or longer. This group was subdivided into 54 infants with 1,105 hemoglobin determinations who had no infections, 45 infants with 1,213 hemoglobin determina-

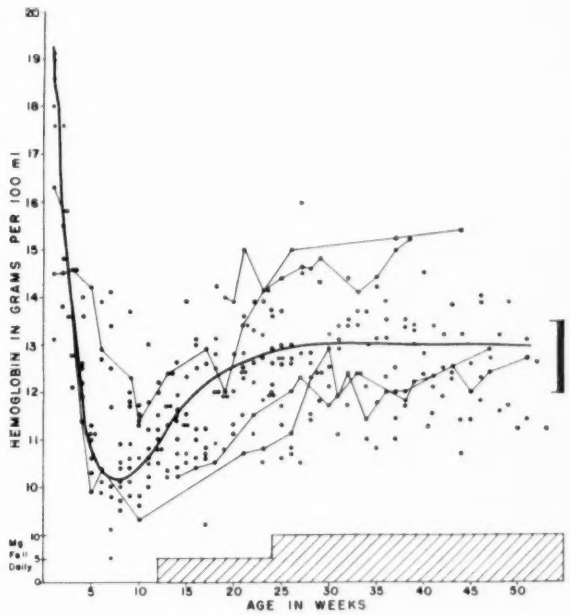

Chart 3.—A scatter pattern of the 305 hemoglobin values for patients receiving ferrous sulfate in the dosage shown. The heavy line represents the mean hemoglobin value of the group and the light lines are values for individual infants. Vertical bar at the right shows the range of values reported by Elvehjem after 26 to 30 weeks of age.

TABLE 6.—*Means, Standard Deviations, and Standard Errors of Means for Groups of Infants as Designated in Tabulation*

Wk.	Group	Classification	Hemoglobin, Gm./100 Ml. Mean	S. D.	S. E. of Mean	No. Determinations
28-29-30	$FeSO_4$	No severe infection	12.7	1.06	0.26	16
37-38-39	$FeSO_4$	No severe infection	13.1	1.24	0.31	16
29	F. A. C.*	No severe infection	11.8	1.37	0.19	52
38	F. A. C.	No severe infection	11.7	1.15	0.20	32
29	F. A. C.	Severe infection	11.7	1.34	0.39	12
37-38	F. A. C.	Severe infection	10.5	1.32	0.31	18

* Ferric ammonium citrate.

26. Hill, A. B.: Principles of Medical Statistics, Ed. 4, London, The Lancet, Ltd., 1948.

tions who had mild infections, and 16 infants with 486 hemoglobin determinations who had severe infections (see above for classification of types of infections). A total of 304 hemoglobin determinations were made on the blood of 18 infants who were fed ferrous sulfate and were observed in the metabolism ward for a similar number of weeks. None of the infants in this group had severe infections. In addition, 53 hemoglobin determinations were made on the 19 infants fed ferrous sulfate who were observed in the well-baby clinic. The hemoglobin values of four infants born prematurely, two followed in the metabolism ward, and two observed in the well-baby clinic, are reported separately. The immature infants in our series consisted of a set of twins and a set of triplets, all of whom were observed in the metabolism ward. Their hemoglobin values are graphed separately. The premature infants were fed ferrous sulfate and the immature infants were fed ferric ammonium citrate.

Chart 1 demonstrates that no difference, graphically or statistically, exists between the hemoglobin value of the two groups of infants fed ferric ammonium citrate, in one of which there were no infections and in the other, mild infections. Therefore, these two groups are combined in the remainder of the discussion. Furthermore, since there were no severe infections in the ferrous sulfate group, all of the values for this group are dealt with in a similar manner.

At 29 weeks of age the mean hemoglobin value of the group of infants given the ferric salts who had no infection was identical to that of those who had severe infection, 11.8 and 11.7 gm. per 100 ml. (Chart 1), respectively. The mean hemoglobin value was significantly higher, 12.7 per 100 ml. (Chart 2) in the group of infants fed ferrous iron. At 38 weeks of age the mean hemoglobin values of the infants given ferrous and ferric iron who had no severe infection were 13.1 (Chart 2) and 11.8 gm. per 100 ml. (Chart 1) respectively, and the difference at both age periods was significant at the 1 per cent level of confidence. These values tend to support the experimental data of Darby and Hahn,[12a] Hahn and Carothers,[12b] and Moore [27] that ferrous iron is utilized more efficiently than ferric iron.

It is well recognized that infection tends to lower the hemoglobin value of infants [6b] and, indeed, at times is the only clinical factor that can be found as the cause of an iron-deficiency anemia. By 30 weeks of age the mean hemoglobin value of the infants with severe infections given ferric iron had decreased to 10.6 gm. per 100 ml. The most severe infections occurred at this period. In the latter weeks of the study the mean hemoglobin value of this group of infants approached 11.5 gm. per 100 ml.

The scatter graph (Chart 3) is informative in that the spread of hemoglobin values of the infants fed ferrous iron is shown. The range of values is indicative of the variation in hemoglobin levels among the group of infants, rather than degree of fluctuation in one infant, as is shown by the light lines indicating values for each of four infants. There is no adequate explanation why hemoglobin values of infants fed similar amounts of iron, living in a controlled environment and receiving carefully constructed diets, might level off at 11.5 gm. or at 13 gm. per 100 ml. after the fourth month of life unless it could be differences in storage of iron during

27. Footnotes 6b and 13.

pregnancy, which is dependent on the maternal diet and the maturity of the infant. A definite trend toward increasing hemoglobin values occurred from the fourth to the sixth month of life, whether the highest level at four months was 11.5 or 13.0 gm. After 6 months of age, very little change was noted in the hemoglobin values obtained from a given infant.

The hemoglobin values of four infants born somewhat prematurely are shown in Chart 4. The smallest infant had a birth weight of 4 lb. 6 oz. (1,980 gm.), so that these infants did not differ markedly from full-term infants. None required transfusions, and with the small amounts of supplemental ferrous iron given, each

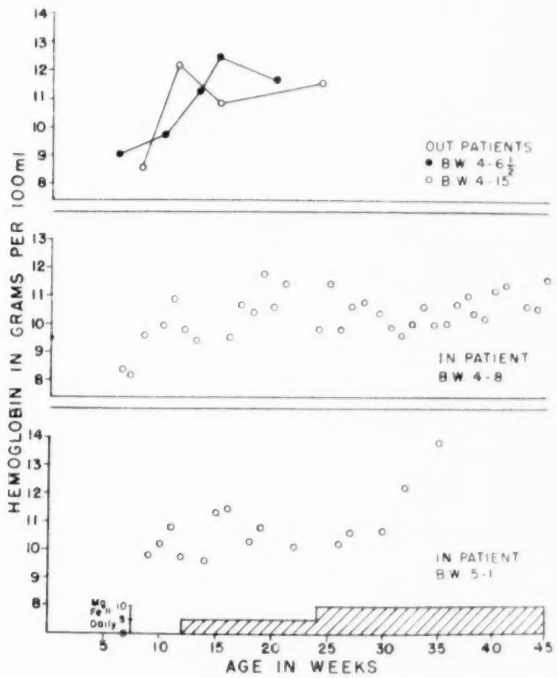

Chart 4.—Hemoglobin values of the four premature infants studied. All received ferrous sulfate in the dosage shown. There is a progressive rise in hemoglobin values. No small premature infants were studied. *B. W.* indicates birth weight in pounds and ounces.

was able to maintain hemoglobin values greater than 10 gm. per 100 ml. There is no agreement as to how soon premature infants are able to utilize supplemental iron in their diets, but evidence is accumulating to the effect that prematurely born infants are able to utilize iron when given in the form of pureed meats as early as the sixth week of extrauterine life.[28]

28. Levine, S. Z.: Protein and Amino Acid Nutrition in Pediatrics and in Pregnancy, in Proteins and Amino Acids in Nutrition, edited by M. Sahyun, New York, Reinhold Publishing Corporation, 1948, Chap. 10. Sisson, T. R. C.; Emmel, A. F., and Filer, L. J., Jr.: Meat in the Diets of Premature Infants, Pediatrics **7**:89, 1951.

All three of the triplets studied (Chart 5) required small whole-blood transfusions at 20 to 25 weeks of age, after which 10 mg. of ferric iron daily sufficed to maintain hemoglobin values above the 10 gm. level. The whole-blood transfusion given the girl twin at 18 weeks of age caused an immediate rise of hemoglobin to 16.2 gm. per 100 ml. The hemoglobin values then decreased in a manner parallel to that of the first eight weeks of postnatal life, thus increasing the amount of stored iron. In retrospect, it might have been the procedure of choice to have given transfusions to the boy twin also. However, he was making a satisfactory weight gain and was suffering apparently no ill effects from the low hemoglobin levels found, and he showed a progressive rise of hemoglobin value in the latter weeks of the study.

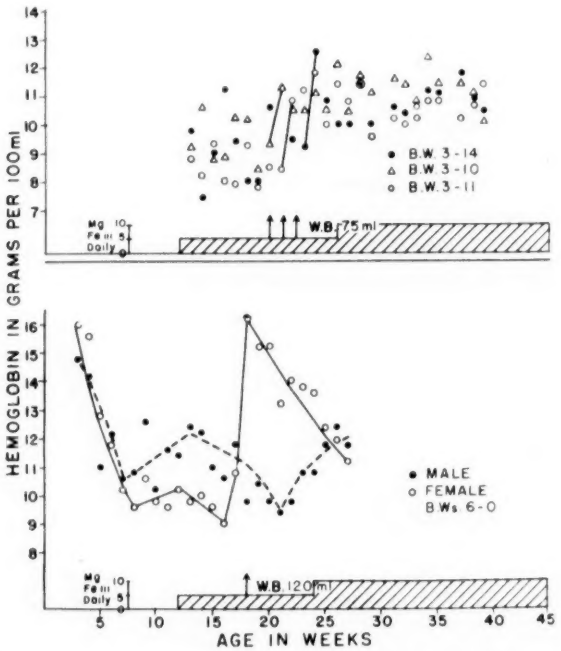

Chart 5.—Hemoglobin values of a set of triplets and a set of twins. Whole blood transfusions were given as shown by the arrows. They all received ferric ammonium citrate supplements to their diets. Note the rapid fall of hemoglobin in the female twin after transfusion and the similarity of slope to the curve plotted at the time of physiological hemolysis of red blood cells shortly after birth.

COMMENT

The published data with which we compare our results are those of Elvehjem [1] of Wisconsin, and Kato [29] of Chicago.

Elvehjem and his group had obtained approximately 2,000 hemoglobin values on 750 children from birth to 5 years of age. The diets of these children were supervised. These infants were seen in the child health centers of Madison, Wis.

29. Kato, K., and Emery, O. J.: Hemoglobin Content of Blood in Infancy: Study of 780 Cases from Birth to 2 Years, with 1,065 Determinations, Folia haemat. **49**:106, 1933.

The mean hemoglobin value for infants at 52 weeks was 11.5 gm. per 100 ml. At the end of the study, 18 children were fed iron supplements consisting of egg yolk at 3 months of age and fortified cereals at 4 months of age. In this group of infants an increase of hemoglobin from an average of 11.5 to an average of 12.4 gm. per 100 ml. was noted. The authors subsequently added 25 mg. of iron as ferric pyrophosphate and 1 mg. of copper as copper sulfate to the diets of a third group of infants of comparable ages and found an elevation of hemoglobin content of the blood from 12.0 to 13.5 gm. per 100 ml. at 52 weeks of age.[1b] The former curve is used in comparison with our data (Chart 1) because weekly results were not listed in the latter article. The range of hemoglobin values reported for the infants given iron and copper will be compared grossly to our ferrous sulfate group (Chart 3).

Kato and Emery [29] studied 180 infants in the age period of birth to 2 years and obtained 1,065 hemoglobin determinations. These infants were not given additional iron, and the diets were not described. The patients were from the lower socioeconomic group of Chicago and were seen in the child-welfare clinics of the University of Chicago or in the newborn service of Cook County Hospitals (Chart 1).

Our standard deviations of the hemoglobin values at 29 and 38 weeks, presented in Table 6, compare favorably with those reported by the above investigators, namely, 1.4 gm. per 100 ml. (Kato at 7 to 8 months and 9 to 12 months); 1.24 (Elvehjem at 24 to 28 weeks), and 1.51 (at 52 to 56 weeks).

No statistical difference exists between the mean hemoglobin values of the group of well infants fed ferric ammonium citrate when compared to those of Elvehjem's series at either 29 or 38 weeks. There is, however, a statistical difference between Kato's values and those of the infants reported herein at these two age periods. This difference is significant at the 1% level of confidence.

Elvehjem's later publication discussed the addition of both 12.5 mg. of iron and 0.5 mg. of copper and also 25 mg. of iron and 1 mg. of copper daily in the form of ferric pyrophosphate and copper sulfate, beginning at 3 weeks of postnatal life. Fifty-five patients were the subjects of this report and were studied in the Dungreen school clinic. He observed a consistent increase of hemoglobin from the previously reported 9 to 11 gm., to 12 to 13.5 gm. per 100 ml. of whole blood with the larger doses given. With the smaller dosage not as consistent or uniform an increase occurred. No tables of data were published in this paper, so a statistical analysis cannot be made. However, it can be seen that with only 10 mg. of iron as ferrous sulfate without added copper we obtained exactly the same hemoglobin values. These results indicate that if copper is needed in addition to that supplied by the diet, the amount required is minute and is provided by the copper-contaminating U. S. P. iron salts. Evidence exists [30] that the absorption of iron is decreased in the presence of excessive phosphate. The choice by Elvehjem's group of a ferric instead of a ferrous salt, and a salt containing phosphate ion may have contributed to the poorer utilization of iron by their subjects. Also much has been written

30. Hegsted, D. M.; Finch, C. A., and Kinney, T. D.: The Influence of Diet on Iron Absorption: The Interrelation of Iron and Phosphorus, J. Exper. Med. **90**:147, 1949. Darby, W. J.: Iron and Copper, Council on Foods and Nutrition, J. A. M. A. **142**:1288, 1950.

lately,[31] in regard to the major role of protein in the manufacture of red blood cells and hemoglobin synthesis. The protein content of the diets fed in Elvehjem's study is not reported. All the infants reported in the present study were artificially fed, and it is the practice in this clinic to offer a high-protein intake of 3 to 4 gm. per kilogram.[28] The high-protein feeding might well be an important factor to explain the satisfactory results obtained with smaller amounts of iron.

Hemoglobin values of infants have shown the customary initial fall from high values (18 to 22 gm. per 100 ml.) to a minimum value at 10 to 12 weeks of age (10.5 to 11.5 gm. per 100 ml.). During the next 10 weeks the usual progressive secondary rise of hemoglobin values is observed. However, after about the 20th week of life a slow secondary fall of hemoglobin occurs, and the values continue to fall slowly throughout the remainder of infancy unless iron-containing foods or medicinal iron is given. If one had only the data of these representative curves of hemoglobin values it would seem likely that the secondary rise indicates utilization of stored iron, and that the secondary fall indicates the need for additional dietary iron, in the form of either iron-containing foods or supplementary elemental iron. The full-term infants in this study receiving small amounts (5 to 10 mg.) of ferric or ferrous iron did not demonstrate the secondary fall of hemoglobin values. The infants with more severe infections showed a progressive slow rise of hemoglobin values during late infancy.

It is often stated [32] that iron is not absorbed when given in milk and with meals high in phytates or phosphates. The small amount of ferrous or ferric iron used in the study was added to the milk, and satisfactory hemoglobin responses were obtained. The iron did not cause changes in the milk and there were no symptoms of gastrointestinal tract intolerance to the preparation used. One major exception should be pointed out, however. At one time the ferric ammonium citrate preparation used in this study was found to be contaminated by mildly pathogenic organisms and was thought to be responsible for a mild epidemic of diarrhea in the metabolism ward. More concentrated ferrous iron solutions have been prepared, such as the one used in this study,[22] which do not support bacterial growth.

CONCLUSIONS AND SUMMARY

One hundred fifteen full-term infants were given ferric iron as ferric ammonium citrate, and 37 full-term infants were given ferrous iron as ferrous sulfate. Seven immature or prematurely born infants were studied. No instance of gastrointestinal irritation due to the iron was observed.

Ferrous iron in the same dosage permitted significantly higher hemoglobin values in well infants than did ferric iron.

The small amounts of iron given daily were sufficient to maintain hemoglobin values at a constant level throughout the latter half of infancy in all full-term

31. Lynch, H. D., and Snively, W. D., Jr.: Hypoproteinosis of Childhood, J. A. M. A. **147**:115, 1951. Stare, F. J., and Thorn, G. W.: Protein Nutrition in Problems of Medical Interest, ibid. **127**:1120, 1945. Jacobs, H. M., and George, G. S.: Evaluation of Meat in the Infant Diet, Pediatrics **10**:463, 1952.

32. McCance, R. A.; Edgecombe, C. N., and Widdowson, E. M.: Phytic Acid and Iron Absorption, Lancet **2**:126, 1943. Footnote 30

infants. Even in those infants who had severe infections, marked anemia did not develop, but hemoglobin values were maintained above 10 mg. per 100 ml.

Prematurely born infants and infants of multiple birth may need more assistance in the prevention of anemia than is provided by these small daily quantities of iron. A small transfusion at 15 to 20 weeks of age was efficacious in bringing the hemoglobin value to near normal, after which 10 mg. of iron daily maintained hemoglobin at normal levels.

This study corroborated the findings of others that severe infectious illness in infancy is accompanied by significant decrease in the hemoglobin level. Mild infections, on the other hand, caused no significant decrease in the hemoglobin level.

The amount of iron storage at birth depends on the adequacy of the mother's diet, the length of gestation, and the watchfulness of the obstetrician that the umbilical cord not be clamped until all pulsations cease, so that the baby receives the maximum amount of blood possible. The infant born at term of a healthy well-fed mother will maintain a good hemoglobin level at least up to 6 months of age. If he receives some iron-containing foods daily after the fourth month of life, probably no other iron supplements are necessary. An infant receiving only the iron of milk generally shows a slow decrease in hemoglobin level during the latter half of infancy and, if his original iron store is poor, an iron-deficiency anemia will occur in late infancy. However, in view of the many variables involved in determining the iron available to the infant and the difficulty in evaluating each variable it seemed wise to study the effect of a daily dosage of iron maintained at a level sufficiently low to be given in the formula. Five milligrams of iron was given daily to infants 3 to 6 months of age and 10 mg. daily to the older infants, which prevented the development of hypochromic anemia.

UNUSUAL MALIGNANT OVARIAN TUMOR IN A YOUNG CHILD

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AND
SIMON KOLETSKY, M.D.
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TUMORS of childhood are always interesting because one feels that the cause of tumor may eventually be solved by the careful study of these cases. Malignant tumors especially attract one's attention and study. We feel that in very young children, no matter what organ may be involved, the cases should be recorded in detail so that eventually the mass of material assembled will help in giving leads that will solve this problem.

Dargeon,[1] of New York, states that in 1940 Kelly reported that among 434 cases of malignant ovarian tumor observed at Memorial Hospital in New York none had occurred before the age of 10 years and only 4 between the ages of 10 and 15 years. Dargeon goes on to discuss 14 previously unreported cases, four in children under 10 years of age, one in a child one year of age. The last was a case of mesonephric adenosarcoma. The patient had a mass in the left lower quadrant, onset two weeks, operation with removal of ovary. The patient died four months following operation.

Teratoma of the ovary in an infant 20 months of age was reported by Garrett.[2] This was reported as successfully removed. The next youngest child with this tumor, for which records were found, was 3 years, and the next ages were 3½, 6, and 6½ years.

Teratoma of the ovary in a 16-month-old child was reported by Gilman, Smith, Puziss, and Karp.[3] This patient came into the hospital following an acute onset of abdominal pain of 24 hours' duration. The presenting symptoms were crying and vomiting. Examination showed a tender mass filling the right side of the abdomen. The ovarian mass was twisted at the time of operation, and both tube and ovary were surgically removed. This patient is stated by the authors to be the youngest in cases on record of proved teratoma of the ovary.

From the Surgical Service and Department of Pathology, The Woman's Hospital, and The Institute of Pathology, Western Reserve University School of Medicine.

1. Dargeon, H. W.: Ovarian Tumors in Childhood, Pediatrics **3**:773-776 (June) 1949.

2. Garrett, S. S.: Teratoma of the Ovary in an Infant 20 Months of Age, Am. J. Dis. Child. **79**:321-323 (Feb.) 1950.

3. Gilman, A.; Smith, J.; Puziss, I., and Karp, L. M.: Teratoma of the Ovary in a Sixteen-Month-old Child, California Med. **75**:105-106 (August) 1951.

Bilateral granulosa cell tumors were successfully removed in a child aged 14 weeks by Zemke and Herrell.[4]

Robinson,[5] in 1923, was the first to publish in the American literature a report of a case of granulosa cell tumor. Further study since shows that 60% of granulosa cell tumors occur after the menopause and 30% between puberty and the climacteric, whereas only 5 to 10% occur before adolescence.

In eight cases out of 160 of a series collected by Bland and Goldstein[6] the ages of the patients were 4, 5, 5, 5, 6, 7, 8, and 9 years respectively, so the youngest as reported was 4 years of age until Zemke and Herrell[4] reported their case of a patient 14 weeks of age. In this case no endocrine studies were done and no hormone studies on urine or blood performed. This patient is the youngest in reported cases of granulosa cell tumor of ovaries in the literature.

Obadelak[7] reported a case of true dermoid of the ovaries at the age of 2 years.

Gittins and Hawksley[8] described a tumor of the ovaries that they felt was a bilateral endothelioma. The patient was a one-year-old child with monocytic leukemia. This classification might be different at the present time but, we feel, this must be included in malignant tumors of ovaries.

Cornil and Schachter[9] described a case of true granulosa cell tumor. Symptoms started at the age of 16 months but were proved to be such at the age of 22 months by operative removal with histological and endocrine confirmation. At the time of the operation the capsule of ovary was intact, yet the child died from the disease from metastasis several months later in spite of surgery and x-ray therapy.

Mayo and Fauster[10] reported a case of a patient one year of age with a large cyst containing 1 liter of fluid and having a solid tumor attached to it, stating this was a carcinoma of the ovary. The diagnosis was probably correct, but it will not fit into the classification of malignant tumors of the ovary as it is known today. This probably was not a granulosa cell tumor. It probably was a papilliferous cyst adenocarcinoma of the ovary.

This covers in review the 10 cases of malignant tumor found in the literature in which the patients were under the age of 2 years.

REPORT OF A CASE

P. M., a 19-month-old baby girl, was admitted to The Woman's Hospital on Dec. 19, 1951. The history given was that the child had not acted right for three weeks and showed signs of an upper respiratory infection with fever. Antibiotics and the usual measures gave no

4. Zemke, E. E., and Herrell, W. E.: Bilateral Granulosa Cell Tumors: Successful Removal from a Child 14 Weeks of Age, Am. J. Obst. & Gynec. **41**:704-707 (April) 1941.

5. Robinson, M. R.: Folliculoid Cancer of the Ovary: A Rare Pathological Entity, Am. J. Obst. & Gynec. **5**:581-600 1923.

6. Bland, P. B., and Goldstein, L.: Granulosa Cell and Brenner Tumors of Ovary: Report of Case with Review of Those Cases Already Recorded, Surg., Gynec. & Obst. **61**:250-266 (August) 1935.

7. Obadalek, W.: Stielgedrehte Eierstockcysten im Kindesalter, Monatsschr. Kinderh. **48**:419-433, 1930.

8. Gittins, R., and Hawksley, J. C.: Ovarian Sarcoma in Children, Arch. Dis. Childhood **7**:335-341 (Dec.) 1932.

9. Cornil, L., and Schachter, M.: On Granulosa Tumors (Folliculomata) of the Ovary in Children and Infants, Med. españ. **6**:355 (Oct.) 1941.

10. Mayo, C. W., and Fauster, J. U., Jr.: Ovarian Tumors of Children, S. Clin. North America **12**:1047-1051 (Aug.) 1932.

relief. A careful physical examination showed a mass in the lower abdomen above the symphysis, not tender to palpation.

On admission, x-ray examination of the colon, the abdomen, the chest, and the skull showed no significant abnormalities.

Laboratory findings were as follows: white blood cell count 9,000; red blood cell count 3,200,000; hemoglobin 55%; urine yellow, cloudy, and acid, with a 1+ reaction for albumin and specific gravity 1.029; microscopic examination showed 2 to 4 white blood cells. The platelet count was normal. The blood type was A, Rh positive.

Following the hospital evaluation and study it was felt advisable to do an exploratory examination on the abdomen, with the diagnosis of ovarian tumor, probably malignant type, because of the anemia of 55%.

The child was given an ether anesthesia Dec. 19, 1951, and laparotomy was performed.

Report of Operation.—Exploratory laparotomy was performed, with excision of bilateral ovarian tumors.

The abdomen was prepared in the usual manner and draped. It was opened through a mid-line infraumbilical incision. When the abdomen was opened and the peritoneal cavity was entered a tumor was found which was too large to be delivered. The incision was extended upward to the right of the umbilicus. This permitted an ovarian tumor 10 to 12 cm.

Fig. 1.—Patient B. M. on second admission to the hospital.

in diameter to be removed. Care was exercised to avoid contamination of the abdomen with what appeared to be a malignant tumor. The ovarian pedicle was clamped and the tumor excised. The pedicle, which included the ovarian ligament, a portion of the Fallopian tube, and a portion of the broad ligament, was sutured. Exploration revealed a similar but smaller tumor of the left ovary. This was removed in a similar manner. No other pathology was found on further exploration. The abdomen was closed in layers.

Following the operation the temperature chart showed an irregular fluctuation up to 104 F. This finally subsided, and the child was discharged on Jan. 11, 1952, for further care in the home and to be closely followed. She did not improve and was returned to the hospital on Jan. 23, 1952.

On this admission it was obvious that the child was in poor condition. She was poorly nourished. The left eyeball and eyelid were swollen. The front part of the head was swollen. The veins stood out on the left side (Fig. 1). The skin was bluish as the disease progressed. There was evidence of metastasis of the skull involving the left eye. X-rays showed an increased bulging of the fontanels and a month later the appearance of metastasis to zygoma on the left side. Finally there was paralysis of the face on the left side. X-rays at no time showed metastasis to the lungs. The child died Feb. 23, 1952, two months following the first admission.

Laboratory findings were as follows: white blood cell count 11,950; red blood cell count 1,500,000; differential count, 44 polymorphonuclear leucocytes, 52 lymphocytes, and 4 mononuclear leucocytes; marked achromia; marked anisocytosis.

Pathological Report.—Simon Koletsky, M. D., Professor of Pathology, Western Reserve University School of Medicine, prepared the pathological report.

He states that the gross specimen consisted of two tumor masses, one from each ovary. Figure 2 shows both tumors of the ovaries, on the external and the cut surfaces.

The mass from the right ovary was roughly round, solid, and measured 11 cm. in diameter and weighed 230 gm. There was an intact capsule which varied from grayish blue to purple in color, and this showed several lobular elevations due to projections of tumor nodules within the main mass. No tumor was present on the outer aspect. The cut surface showed a bulging soft fleshy solid neoplasm with no cystic change, with considerable hemorrhage, and with color varying from pinkish white to purplish red. The connective tissue stroma was usually scant except for a few places which showed lobulation of the tumor owing to strands of dense gray fibrous tissue.

The mass from the left ovary measured 5 cm. in diameter and weighed 40 gm. The outer aspect was similar in appearance to that of a larger tumor. The cut surface was also similar except for less hemorrhagic change.

Fig. 2.—External and cut surfaces of ovarian tumors from patient B. M.

Microscopic Description.—Microscopically, numerous sections from both neoplasms showed groups of discretely arranged fairly large round or irregular cells of epithelial type with large vesicular nuclei and moderately abundant cytoplasm. Mitoses were numerous and cellular pleomorphism moderate to marked. The cells were frequently arranged in clusters around cyst-like spaces (Fig. 3) and sometimes arranged in anastomosing columns (Fig. 4). The connective tissue stroma varied from scant to fairly abundant. There was no glandular pattern. Regions of hyperemia, hemorrhage, and necrosis were frequent. There was no invasion of the outer portion of the capsule. Special stains for fat were negative.

The microscopic diagnosis was undifferentiated carcinoma of both ovaries, probably granulosa cell type.

Vaginal Smear.—On Feb. 15, 1952, a Papanicolaou vaginal smear was taken. The report "shows only a very few keratinized cells. (With estrogen effect there should be about 40 to 50% keratinized cells.)"

Chemical Hormone Studies on Urine.—There were 17-ketosteroids in the urine. On Feb. 20, 1952, a 24-hour urine specimen was collected for ketosteroid chemical studies. This was found to be 12.8 mg. per liter, which is within normal limits.

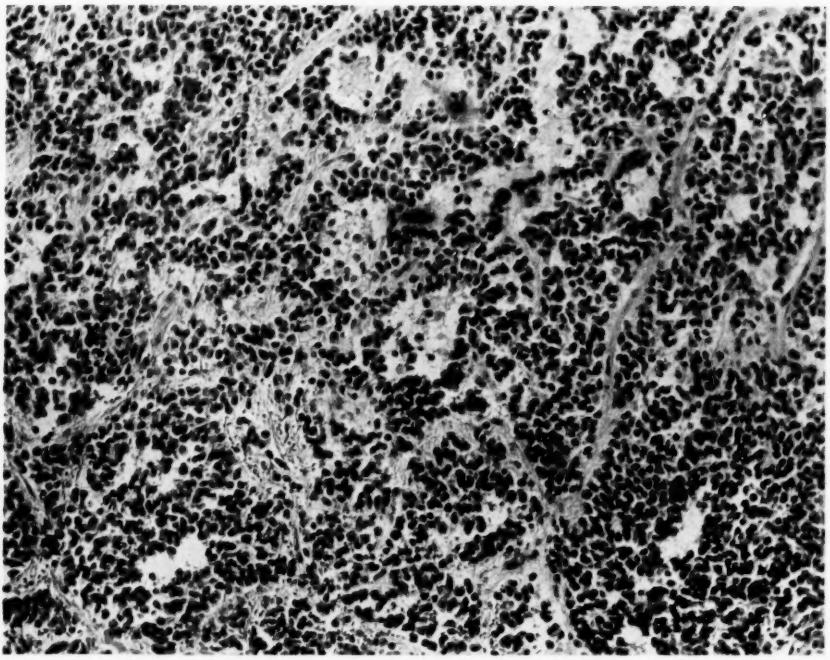

Fig. 3.—Ovarian tumor. Cells are arranged in clusters around cyst-like spaces. Hematoxylin-eosin stain (× 150).

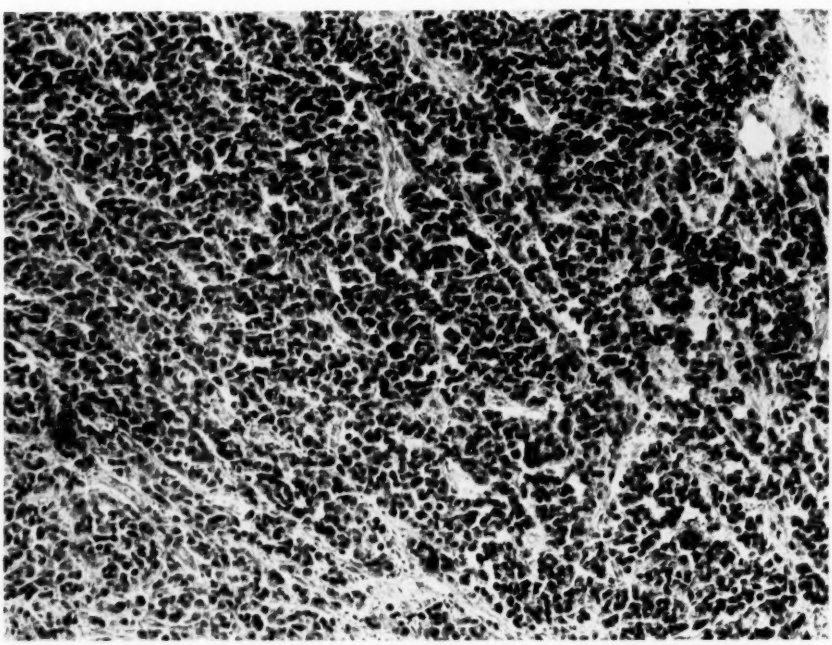

Fig. 4.—Ovarian tumor. Cells are arranged in anastomosing columns. Hematoxylin-eosin stain (× 150).

Summary in tabular form of the reported cases in the literature of malignant ovarian tumors in children under the age of 2 is as follows:

Author	Age, Yr.	Type
Obadalek [7]	2	Dermoid
Gittins and Hawksley [8]	1	Endothelioma bilateral and monocytic leukemia
Mayo and Fauster [10]	1 5/12	Carcinoma
Del Compo [9]	2	Dermoid
Dargeon [1]	1	Mesonephric adenosarcoma
Gilman, Smith, Puziss, and Karp [3]	1 4/12	Teratoma
Garrett [2]	1 8/12	Teratoma
Zemke and Herrell [4]	4/12	Bilateral granulosa cell tumor
Garrett [2]	1 8/12	Teratoma of ovary
Cornil and Schachter [6]	1 10/12	Granulosa cell tumor right ovary, left normal
Einsel, Bowman, and Koletsky	1 7/12	Granulosa cell type of both ovaries

[9] An. Fac. Med. Montevideo 17:149, 1932.

COMMENT

This type of case is always a diagnostic problem for, the child being under 2 years of age, it is impossible to obtain a history from the child. Therefore, the information must be a study of the abnormal behavior and the outward manifestation of abnormal conditions. The parents, if observing, usually bring the child early for examination, for they realize that there is something seriously wrong. One might summarize the diagnostic procedure as follows:

1. The first thing is the appearance of the child—almost all show an advanced anemia. (Acute onset usually means volvulus of the ovary with strangulation and gangrene. This turns the case into an emergency operative procedure.)

2. If careful physical examination is performed, a tumor mass is found in the abdomen. It may be tender or not tender.

3. X-ray of abdomen is done. Flat plate may visualize the tumor if it is large. It is necessary also to see if there is an encroachment on or a displacement of the viscera.

4. Rectal examination will give information on small firm ovarian tumors and always should be performed with the other hand palpating the abdomen.

5. X-ray of distant locations such as the bones and chest should be done for evidence of metastasis, if present, will confirm the presence of a malignant tumor.

6. Therapy is always radical surgery to be followed by x-ray therapy.

7. It is necessary to be alerted always to this possibility in an obscure puzzling disease of a girl child. Then fewer cases will be missed when a decision must be made in this type of case.

Granulosa cell tumors usually produce dramatic physical alteration. This includes advanced body growth, lower abdominal or pelvic mass, hypertrophy of the breasts, enlarged nipples, pubic hair and labia enlarged, precocious menses, and a great increase in estrogen excretion. Fourteen weeks is the age of the youngest patient in reported cases of this tumor. Between 5 and 10% occur before puberty. They are usually not bilateral. The tumors in 5% of cases are bilateral no matter what the age is.

CONCLUSIONS

This is a report of the second youngest patient with malignant granulosa-cell tumor of the ovary in cases reported in the literature, with a review of the malignant tumors of children under the age of 2 years.

GROWTH AND METABOLISM IN NORMAL AND THYROID-ABLATED INFANT RHESUS MONKEYS (MACACA MULATTA)

VI. Iodine Metabolism in Normal and Thyroid-Ablated Infant Rhesus Monkeys (Macaca Mulatta)

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As one of a series of integrated reports regarding the role of thyroid in growth and metabolism of normal and I^{131} thyroid-ablated infant rhesus monkeys,[1] this communication presents quantitative aspects of iodine metabolism.

Earlier reports of thyroid function in rhesus monkeys are limited to observations on thyroidectomized mature animals,[2] except in the study of Fleischmann and

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These investigations were principally supported by a research grant from the Playtex Park Foundation and also received support from the grant of the Jefferson Macleod Moore Estate to the University of California Medical School.

1. (*a*) Pickering, D. E.; Smyth, F. S.; van Wagenen, G., and Fisher, D. A.: Growth and Metabolism in Normal and Thyroid-Ablated Infant Rhesus Monkeys (Macaca Mulatta): I. Growth and Metabolism in Normal Infant Rhesus Monkeys (Macaca Mulatta), A. M. A. Am. J. Dis. Child. **86**:1, 1953. (*b*) Pickering, D. E., and Fisher, D. A.: II. Growth and Metabolism in Thyroid-Ablated Infant Rhesus Monkeys (Macaca Mulatta), ibid. **86**:11, 1953. (*c*) III. Growth and Metabolism Following *l*-Thyroxine Administration in Thyroid-Ablated Infant Rhesus Monkeys (Macaca Mulatta), ibid. **86**:147, 1953. (*d*) Pickering, D. E.; Fisher, D. A., and Scott, K. G.: IV. Radiosodium (Na^{24}) Space in Normal and Thyroid-Ablated Infant Rhesus Monkeys (Macaca Mulatta), ibid. **86**:157, 1953. (*e*) Lusted, L.; Pickering, D. E.; Fisher, D. A., and Smyth, F. S.: V. Roentgenographic Features of Skeletal Development in Normal and Thyroid-Ablated Infant Rhesus Monkeys (Macaca Mulatta), ibid. **86**:426, 1953. (*f*) Crane, J.; Pickering, D. E., and Smyth, F. S.: VII. Histopathology of Normal and Thyroid-Ablated Infant Rhesus Monkeys (Macaca Mulatta), ibid., to be published.

2. (*a*) Fleischmann, W.; Shumacker, H. B., Jr., and Straus, W. L., Jr.: Influence of Age on the Effect of Thyroidectomy in the Rhesus Monkey, Endocrinology **32**:238, 1943. (*b*) Vincent, S., and Jolly, W. A.: Some Observations upon the Functions of the Thyroid and Parathyroid Glands, J. Physiol. **32**:65, 1904; (*c*) Further Observations upon the Functions of the Thyroid and Parathyroid Glands, ibid. **34**:295, 1906. (*d*) Carlson, A. J., and Woelfel, A.: On the Internal Secretion of the Thyroid Gland, Am. J. Physiol. **26**:32, 1910. (*e*) Halpenny, J., and Gunn, J. A.: Note on Extirpation of the Thyroid Gland in Monkeys, Quart. J. Exper. Physiol.

(Footnotes continued on next page)

co-workers,[2g] where two 8-month-old animals were also observed. Of the reported studies,[2] none have dealt with iodine metabolism per se, nor have they been concerned with the role of thyroid in growth and development. In all cases, thyroidectomy was achieved either by prolonged administration of thiouracil [3] or by surgical means—the latter frequently being complicated by severe and often fatal hypoparathyroidism.[4] When thiouracil was used, large doses (0.8 gm. per day) were found necessary to produce hypothyroidism and thyroid hyperplasia in adult animals, and its use was commonly complicated by granulocytopenia.[5] A number of authors reported that ostensibly complete thyroidectomy in adult animals produced few if any changes,[6] while others have described mild myxedema.[7] Hypercholesteremia, slowing of circulation time, increased ability to retain exogenous creatine, and prolongation of intervals between menstruation have also been reported.[8]

At^{211} (Element 85) was used in initial attempts at thyroid ablation, but its use was also complicated by marked granulocytopenia. It was, therefore, abandoned in favor of I^{131}.[1b] Ablation with I^{131} was found to be uniformly successful and without complication. Thyroid ablation was confirmed by I^{131}-uptake studies, serum butyl-extractable iodine determinations, and histological absence of thyroid tissue in two animals electively sacrificed. Parathyroid integrity, implied by the absence of clinical and biochemical signs of hypoparathyroidism, was confirmed with identification of normal parathyroids in the animals sacrificed.[9] The profound physical, growth, metabolic, skeletal, and histological effects of I^{131} thyroid ablation in these infants, as well as the response of those features to *l*-thyroxine therapy, are presented in other communications in this series.[10]

METHODS AND MATERIALS

General.—I^{131} used in these studies was procured from the Oak Ridge National Laboratory. Thyroxine used was either crystalline *l*-thyroxine (provided through the courtesy of Dr. H. Roebling Knoch, Director of Specialty Division, Smith, Kline & French Laboratories, Philadelphia) or I^{131}-labelled thyroxine, biosynthesized in this laboratory. All monkeys employed in these studies were selected from the indoor macaque colony raised by one of us (G. van W.). Techniques of care, feeding, and general metabolic study have been previously reported.[11]

4:237, 1911. (*f*) Jailer, J. W.; Sperry, W. M.; Engle, E. T., and Smelser, G. K.: Experimental Hypothyroidism in the Monkey, Endocrinology **35**:27, 1944. (*g*) Burford, T. H.; Allen, E., and Diddle, A. W.: Effect of Total Thyroidectomy upon Experimentally Induced Menstruation in Mature Ovariectomized Monkeys, Endocrinology **20**:635, 1936. (*h*) Aranow, H., Jr.; Engle, E. T., and Sperry, W. M.: Some Effects of the Administration of Thiouracil to Monkeys, Endocrinology **38**:331, 1946. (*i*) Engle, E. T., and Aranow, H., Jr.: Hyperplasia of the Thyroid Gland of Rhesus Monkeys After Thiouracil Treatment, Endocrinology **38**:325, 1946. (*j*) Engle, E. T.: The Effect of Hypothyroidism on Menstruation in Adult Rhesus Monkeys, Yale J. Biol. & Med. **17**:59, 1944.

3. Footnote 2 *h*, *i*, and *j*.
4. Footnote 2 *a*, *b*, *c*, *d*, *e*, *f*, and *g*.
5. Footnote 2 *i* and *j*.
6. Footnote 2 *e* and *f*.
7. Footnote 2 *f*, *g*, *h*, *i*, and *j*.
8. Footnote 2 *f*, *h*, and *j*.
9. Footnote 1 *b* and *f*.
10. Footnote 1 *b*, *c*, *d*, *e*, and *f*.
11. Footnote 1 *a*, *b*, *c*, and *d*.

I^{131}-Uptake Studies.—The scintillation counter described in a previous communication [11] was employed in all I^{131}-uptake studies. Gamma rays incident to I^{131} nuclear disintegration were measured as counts over specific anatomical regions (thyroid, thigh, abdomen). Areas were counted at a uniform distance and aligned to a collimated lead cone interposed between the tissue site and the copper-shielded thallium-activated sodium iodide crystal. At each time interval during the study, an aliquot of administered I^{131} solution was routinely counted with tissue sites, thereby eliminating the otherwise essential corrections for I^{131} physical decay and variation in sensitivity of the counting equipment.

Serum-Precipitable Iodine Studies (Butyl-Extractable Iodine).—Butyl-extractable iodine was determined by the technique of Man,[12] except where I^{131}-labelled thyroxine was involved. In the latter studies, the Man technique was followed through normal-butanol extraction and washing with sodium hydroxide-sodium carbonate. Fractions so obtained were then counted according to techniques described.[11]

Biosynthesis, Extraction, and Identification of I^{131}-Labelled Thyroxine.—Ten female Sprague-Dawley young-adult rats were injected intraperitoneally with a total of 1.6 mc. of I^{131} in isotonic carrier-free solution. Twenty-four hours later their thyroids were extirpated, stripped of connective tissue, and ground in a motor-driven mortar and pestle with 100 mg. papain (Caroid) in approximately 10 ml. 0.85% sodium chloride. The thyroglobulin-papain mixture was then incubated in a constant-temperature water bath at 37 C. for four hours with continuous stirring, and after acidification with 0.5 ml. of 10% sulfuric acid, the digest mixture was subjected to two normal-butanol extractions of 10 and 15 ml., respectively. Following the addition of another 0.5 ml. sulfuric acid a third extraction was made with an additional 10 ml. normal-butanol. The total normal-butanol extract was then centrifuged for 10 minutes at 3,500 rpm. Thyroxine was obtained as an eluate of the normal-butanol extract by subjecting the extract to two 20-ml. washings with a 4-normal sodium hydroxide-5% sodium carbonate solution. The washings carried off elemental iodide, monoiodotyrosine and diiodotyrosine, leaving thyroxine as the sole iodine-containing compound in normal-butanol. The quantity of I^{131}-labelled thyroxine in the final normal-butanol extract was calculated to be approximately 7 γ with specific radioactivity of 300,000 counts per second per microgram. Calculations were based upon the weight, iodine content, and thyroxine content of rat thyroid,[13] and radioactivity of fractions described.

In preparation for its injection, additional steps were taken to separate labelled thyroxine from normal-butanol. For this, the solution was slowly acidified with 4-normal hydrochloric acid, then washed twice with 25 ml. distilled water. The rinse was found to be free of radioactivity. Following adjustment of the pH to 6.0 by addition of 25 ml. of 1.5% sodium bicarbonate, the product was lyophilized to dryness and then dissolved in 100 ml. of sterile 1.5% sodium bicarbonate solution. Reextraction of the final sodium bicarbonate-thyroxine solution resulted in approxi-

12. Man, E. B.; Kydd, D. M., and Peters, J. P.: Butanol-Extractable Iodine of Serum, J. Clin. Invest. **30**:531, 1951.

13. Remington, R. E.; Remington, J. W., and Welch, S. S.: The Thyroid Gland of the Normal Rat: Size, Dry Matter and Iodine Content, Anat. Rec. **67**:367, 1937.

mately 95% recovery of I^{131} counts as thyroxine. No toxic signs were observed when 1-ml. aliquots of the final solution were intravenously administered in healthy adult Sprague-Dawley rats.

Aliquots taken during each step in the extraction of I^{131}-labelled thyroxine, prior to lyophilization, were studied by filter paper chromatography. Resultant chromatograms were radioautographed for convenience in spot identification and presentation. Spot identification was established in earlier studies by comparing chromatograms of the eluted materials with known samples of iodide, monoiodotyrosine, diiodotyrosine and *l*-thyroxine, using the ninhydrin reaction for spot development with the last three substances mentioned.

Samples of parent solutions were placed in their respective columns on the line of origin using a 27-gauge needle and a tuberculin syringe. The paper was suspended from the top of a closed jar with the base immersed in ammonia-propanol

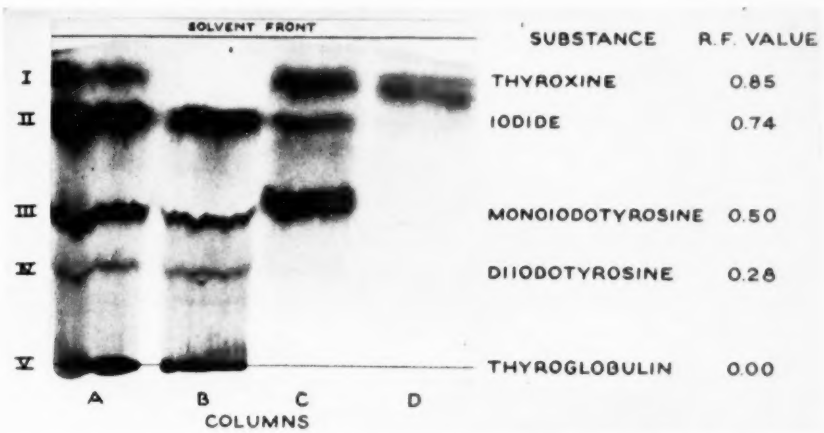


Fig. 1.—Radiochromatograph of biosynthesis (I^{131}-tagged thyroxine during extraction procedures). Radioautographed paper chromatographs of *A*, crude I^{131}-tagged thyroglobulin papain digest, *B*, digest residue after its extraction with *n*-butanol, *C*, *n*-butanol extract of thyroglobulin digest, and *D*, *n*-butanol extract after its extraction with NaOH-Na_2CO_3 solution.

solvent. The solvent was prepared by adding 100 ml. of 0.5% ammonium hydroxide to 200 ml. normal propyl alcohol. The closed jar was allowed to remain at room temperature until ascent of the fluid front was completed, following which the paper was dried in a hood overnight at room temperature. Spots were developed with ninhydrin and the papers radioautographed by exposure of x-ray film. A representative radioautograph of a chromatogram so prepared is presented in Figure 1. "RF values" (spot distance from line of origin divided by fluid front distance from the line of origin) were used for identification of spots.

RESULTS AND COMMENT

Extrathyroidal Inorganic Iodine.—Investigations relating to factors affecting iodine uptake and organic binding by thyroid are discussed. When carrier-free I^{131} in tracer quantities (5 to 15 μc) was injected intraperitoneally, it was observed to accumulate in the thyroid or undergo renal excretion. Binding and release of I^{131} by thyroids of normal animals assumed a strikingly constant pattern. Twenty

uptake studies in six normal animals between 2 and 10 months of age are presented with 12 additional studies conducted in four athyroid animals (between ages 3 and 8 months) over a five-month period (Fig. 2).

In the athyroid group the per cent uptake of I^{131} measured as counts over the anatomical region of thyroid was equivalent to thigh counts. This observation supports other evidence of complete I^{131} thyroid ablation,[9] and justifies use of the difference between thigh and thyroid counts as a measure of thyroid uptake in the normal animals. For as long as 36 hours following the intraperitoneal administration of I^{131}, counts over the abdomen exceeded thigh counts—a fact contributing to continued and slightly increased I^{131} uptake and binding by thyroids of normal animals between 24 and 48 hours. Per cent I^{131} uptake by thyroid in normals

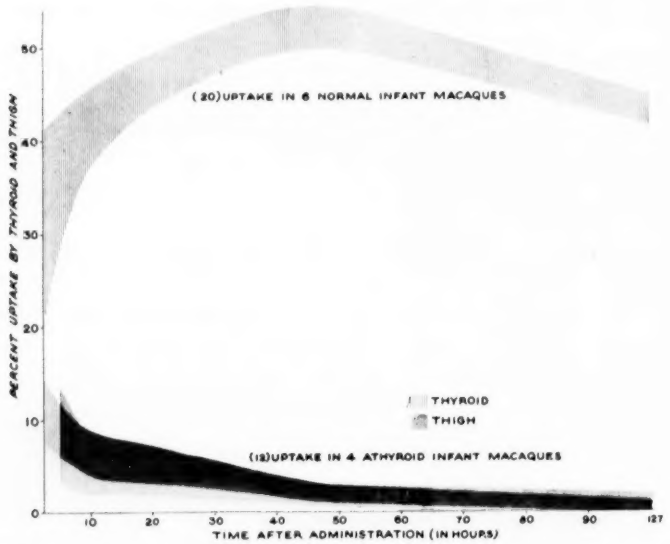


Fig. 2.—I^{131} uptake by thyroid in normal and athyroid macaque infants.

decreased with age; in animals approaching one year, it was found to range from 25 to 30%.

Release of bound I^{131} by thyroid consistently averaged less than 4% per day. The potential quantity of hormone which thyroid can produce in any period by uptake and organic binding of iodine greatly exceeds the uniform quantity released by the gland to serve metabolic needs. A similarly large hormonal reserve with a small, and more or less constant, rate of release by thyroid is described for man.[14]

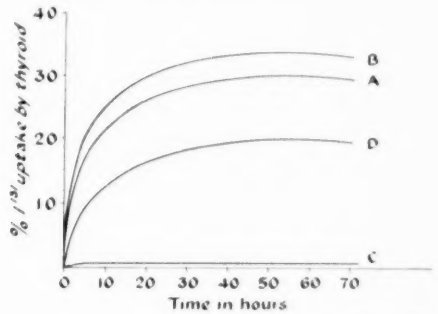
Selected factors affecting pituitary-thyroid homeostasis are described. Effects of exogenous thyrotropic hormone[15] and/or thyroxine on I^{131} uptake by the thyroid

14. Kelsey, M. P.; Haines, S. F., and Keating, F. R., Jr.: Endocrine Review: Radioiodine in the Study and Treatment of Thyroid Disease; A Review, J. Clin. Endocrinol. **9**:171, 1949. Burns, F. J.; Fish, W. A.; Hackett, J. W., and Hickey, F. C.: Radioactive Decay and Metabolic Loss of Iodine from Normal Thyroid, J. Appl. Physiol. **4**:15, 1951.

15. Thyrotropic hormone, a lyophilized pyrogen-free product, was furnished through the courtesy of The Armour Laboratories, Chicago.

of one normal animal were studied over a two-month period, between 10 and 12 months of age (Fig. 3). They are representative of similar studies in other colony members.

Study C, Figure 3, illustrates the nearly complete suppression of I^{131} uptake by thyroid which followed the single administration of 250 γ per kilogram of body weight of *l*-thyroxine. Though present when I^{131} uptake was studied beginning 1 to 4 days following administration of thyroxine, that effect had dissipated by 10 days (Study A, Fig. 3). Correlation with serum butyl-extractable iodine concentration was striking, since the latter was 4 to 5 times normal during the first few days following thyroxine administration and had receded to normal by 10 days



Study	Therapy: Thyroxine 250γ/kg	Therapy: TSH*	Onset of study (days) (relative to thyroxine admin.)
A	0	0	Before or 5-10 days following
B	0	+	Before
C	+	0	Day following
D	+	+	Day following

*TSH 2mgm/kg IM 12 hrs 4 times before onset of study

Fig. 3.—Effect of thyrotropic hormone (T.S.H.), thyroxine, and thyroxine plus thyrotropic hormone on I^{131} uptake by thyroid in normal macaque monkeys.

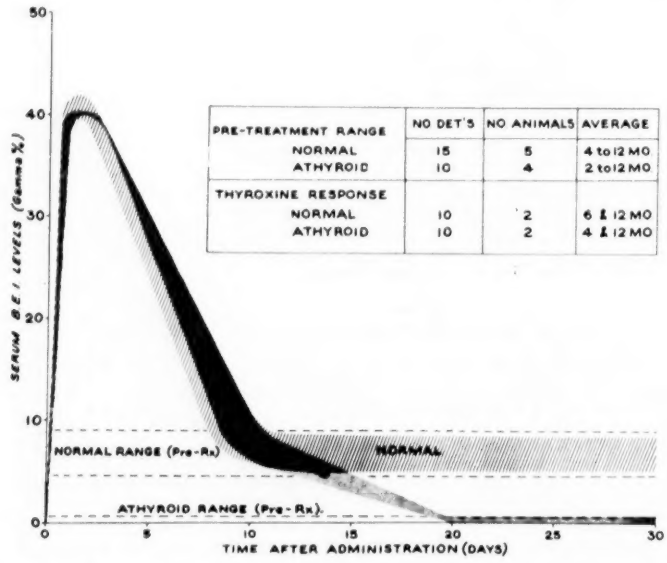
(Fig. 4). High plasma concentrations of thyroxine had effected thyroid I^{131}-uptake suppression chiefly through inhibition of pituitary release of thyrotropic hormone, since concurrent administration of exogenous thyrotropic hormone effected a continued ability of thyroid to concentrate and bind I^{131} (Study D, Fig. 3). Thyrotropic hormone in equal quantity, administered in the absence of thyroxine suppression, was shown capable of stimulating the thyroid to greater than normal I^{131} uptake (Study B, Fig. 3). Exogenous thyroxine and thyrotropic hormone, in like combinations, have been observed to similarly affect I^{131} uptake by thyroid in the rat [16] and in man.[17]

16. (*a*) Taurog, A.; Chaikoff, I. L., and Feller, D. D.: The Mechanism of Iodine Concentration by the Thyroid Gland: Its Non-Organic Iodine-Binding Capacity in the Normal and Propylthiouracil-Treated Rat, J. Biol. Chem. **171**:189, 1947. (*b*) Vanderlaan, W. P., and Greer, M. A.: Some Effects of the Hypophysis on Iodine Metabolism by the Thyroid Gland of the Rat, Endocrinology **47**:36, 1950. (*c*) Halmi, N. S.; Spirtos, B. N.; Bogdanove, E. M., and Lipner, H. J.: A Study of Various Influences on the Iodine Concentrating Mechanism of the Rat Thyroid, ibid. **52**:19, 1953.

(Footnote continued on next page)

Below-normal plasma concentrations of thyroxine effect a reciprocal response by the pituitary. The use of thiouracil and its derivatives is classically known to be followed by reduced plasma thyroxine concentration. Salient features of its mechanisms are classically illustrated by studies in the rat. These have shown that thiouracil administration is followed by suppression of thyroid function with respect to organic binding of iodide and its consequent release as thyroxine, hypothyroidism, and secondary thyroid hyperplasia.[18] Thyroid hyperplasia with hypothyroidism has been reported following administration of thiouracil to adult macaque monkeys.[19]

The increased pituitary activity which followed reduced thyroxine concentration secondary to I^{131} thyroid ablation in animals of this series resulted in marked pituitary enlargement with anterior-lobe beta-cell hypertrophy and vacuolization.[17]



PRE-TREATMENT RANGE	NO DET'S	NO ANIMALS	AVERAGE
NORMAL	15	5	4 to 12 MO
ATHYROID	10	4	2 to 12 MO
THYROXINE RESPONSE			
NORMAL	10	2	6 & 12 MO
ATHYROID	10	2	4 & 12 MO

Fig. 4.—Serum butyl-extractable iodine levels after administration of *l*-thyroxine in normal and athyroid macaque infants.

17. Pickering, D. E., and Miller, E. R.: Thyrotropic Hormone in Infants and Children: Differentiation Between Primary and Hypopituitary Hypothyroidism, A. M. A. Am. J. Dis. Child. **85**:135, 1953. Werner, S. C.; Hamilton, H., and Nemeth, M.: Graves' Disease: Hyperthyroidism or Hyperpituitarism? J. Clin. Endocrinol. **12**:1561, 1952. Danowski, T. S.; Huff, S. J.; Tarail, R.; Wirth, P.; Peters, J. H.; Mateer, F. M., and Garver, K.: Serum Protein-Bound Iodine During Ingestion of Desiccated Thyroid, ibid. **12**:1572, 1952. Querido, A., and Stanbury, J. B.: The Response of the Thyroid Gland to Thyrotropic Hormone as an Aid in the Differential Diagnosis of Primary and Secondary Hypothyroidism, ibid. **10**:1192, 1950.

18. Franklin, A. L.; Lerner, S. R., and Chaikoff, I. L.: The Effect of Thiouracil on the Formation of Thyroxine and Diiodotyrosine by the Thyroid Gland of the Rat with Radioactive Iodine as an Indicator, Endocrinology **34**:265, 1944. Footnote 16 *a*. Astwood, E. B., and Bissell, A.: Effect of Thiouracil on the Iodine Content of the Thyroid Gland, Endocrinology **34**:282, 1944. Danowski, T. S.; Huff, S. J.; Wirth, P. M.; Hill, B. S.; Green, M. H., and Fetterman, G. H.: Protein-Bound Iodine in Serum of Rats Receiving Iodide or Iodine With or Without Goitrogen, J. Clin. Endocrinol. **11**:1254, 1951.

19. Footnote 2 *h* and *i*.

Similar functional and histological hypophyseal changes have been well documented in athyrotic rats[20] and humans.[21] The basis for pituitary-thyroid homeostasis rests, at least in part, upon the described effect of low levels of serum thyroxine in bringing about increased release of thyrotropic hormone by the pituitary, combined with the decreased thyrotropic hormone release which follows greater than normal thyroxine levels.

Thyroid Hormone and Thyroxine.—Organic iodine is an essential integral among protean elements supporting growth, development, and general tissue metabolism. In subsequent paragraphs, investigations are presented to clarify selected quantitative aspects relative to its distribution and fate and daily requirements in normal and athyroid immature macaque monkeys. Data pertaining to concentration of organic iodine of plasma (butyl-extractable iodine) are presented in Figure 4.

Butyl-extractable iodine concentration in plasma of normal animals between 4 and 12 months of age ranged from 4 to 8 γ per 100 cc. A comparable range has been found to exist in sera of normal infants and children after 2 to 3 months.[22] Serum concentration in the newborn child is equal to that in the mother; it then increases to greater than 10 γ per 100 cc. by one week, and subsequently drops to normal by 8 to 10 weeks.[23] In the present series, butyl-extractable iodine concentrations were highest during the younger age period, and by 12 months were consistently in the lower range—4 to 5 γ per 100 cc. By 30 days following I^{131} thyroid ablation, concentration had dropped below 1 γ per 100 cc. in all cases. In normal or athyroid animals, the single intramuscular administration of 250 γ per kilogram of *l*-thyroxine was followed by an increased concentration to approximately 40 γ per 100 cc. within 24 hours. Thereafter, in both groups, concentration fell within the normal range by 10 days and in the athyroid group declined to the pretreatment level by 20 days. Coincident to the above, the athyroid animals experienced transient changes which included clearing of myxedema, increased voluntary food intake and nitrogen and phosphorus retention, creatinuria, and some growth.[24]

Based upon reported calculations from the above studies,[16] athyroid animals were treated over a four-month period with either 6 or 20 γ per kilogram per day of *l*-thyroxine. Therapy with 6 γ per kilogram per day was found capable of reversing general growth and metabolic changes, except for those of the skeletal system, while

20. Koneff, A. A.; Van Dyke, D. C., and Evans, H. M.: Increase in the Thyrotropic Hormone Content of Blood After Thyroidectomy as Shown by Parabiosis, Endocrinology **51**:249, 1952.

21. Hertz, S., and Oastler, E. G.: Assay of Blood and Urine for Thyreotropic Hormone in Thyrotoxicosis and Myxedema, Endocrinology **20**:520, 1936. Rawson, R. W., and Starr, P.: Direct Measurement of Height of Thyroid Epithelium: Method of Assay of Thyrotropic Substance; Clinical Application, Arch. Int. Med. **61**:726, 1938.

22. (*a*) Man, E. B.; Culotta, C. S.; Siegfried, D. A., and Stilson, C.: Serum Precipitable Iodines in Recognition of Cretinism and in Control of Thyroid Medication, J. Pediat. **31**:154, 1947. (*b*) Starr, P.; Petit, D. W.; Chaney, A. L.; Rollman, H.; Aiken, J. B.; Jamison, B., and Kling, I.: Clinical Experience with Blood Protein-Bound Iodine Determination as a Routine Procedure, J. Clin. Endocrinol. **10**:1237, 1950. (*c*) Danowski, T. S.; Johnson, S. Y.; Price, W. C.; McKelvy, M.; Stevenson, S. S., and McKluskey, E. R.: Protein-Bound Iodine in Infants from Birth to One Year of Age, Pediatrics **7**:240, 1951. (*d*) Man, E. B.; Pickering, D. E.; Walker, J., and Cooke, R. E.: Butanol-Extractable Iodine in the Serum of Infants, ibid. **9**:32, 1952.

23. Footnote 22 *c* and *d*.

24. Footnote 1 *b* and *c*

20 γ per kilogram per day induced normal growth of the skeletal system as well.[1c] Serum butyl-extractable iodine concentration found during prolonged administration of 6 and 20 γ per kilogram per day are presented (Fig. 5).

Recent clinical trials have shown crystalline *l*-thyroxine to be an excellent therapeutic agent for treating hypothyroidism in human infants, children, and adults.[25] It has been found to be of equal potency whether administered as *l*-thyroxine, sodium-*l*-thyroxine, or disodium-*l*-thyroxine,[26] and when given orally approximately two-thirds is considered to be absorbed in the rat[26] and in man.[25b] From the present studies it would appear that therapy in athyroid infants and children should be pushed to a limit producing normal serum butyl-extractable iodine concentrations and/or osseous development. Clinical recognition of the importance of osseous development as a guide to optimal therapy in cretin children was first pointed out by Wilkins in 1938.[27]

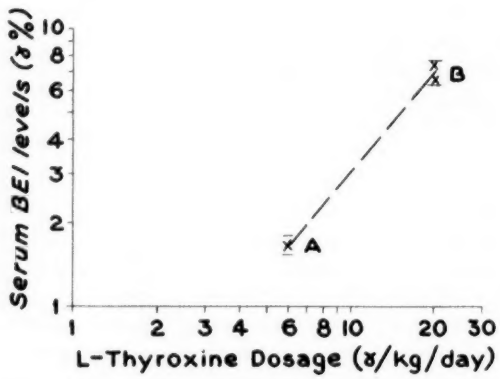


Fig. 5.—Amount of *l*-thyroxine per kilogram of body weight per day required to maintain blood levels in athyroid macaque monkeys.

Some definition of the volume of distribution of thyroxine and its rate of biological decay was accomplished by studies following its administration as an I^{131}-labelled product. Approximately 0.5 γ I^{131}-labelled thyroxine (containing 150,000 counts per second) was administered intravenously in one untreated athyroid and one euthyroid macaque. That dose was less than 10% of the calculated daily requirement, and therefore served only to tag existing extrathyroidal hormone.

25. (*a*) Hart, F. D., and Maclagan, N. F.: Oral Thyroxine in Treatment of Myxoedema, Brit. M. J. **1**:512, 1950. (*b*) Salter, W. T., and Rosenblum, I.: Oral Sodium L-Thyroxine in the Treatment of Myxedema and Cretinism, Am. J. M. Sc. **224**:628, 1952. (*c*) Papper, S.; Burrows, B. A.; Ingbar, S. H.; Sisson, J. H., and Ross, J. F.: The Effects of L-Thyroxine Sodium on Nontoxic Goiter, on Myxedema and on the Thyroid Uptake of Radioactive Iodine, New England J. Med. **247**:897, 1952. (*d*) Salter, W. T.; de Visscher, M.; McAdams, G. B., and Rosenblum, I.: Changes in Blood Iodine Fractions and Radioactivity Under Therapy, J. Clin. Endocrinol. **11**:1512, 1951.

26. Littrell, J. L.; Kelsey, C.; Dolgin, A., and Fevold, H. L.: Comparative Activities of Thyroxine and Its Monosodium and Disodium Salts, Proc. Soc. Exper. Biol. & Med. **81**:670, 1952.

27. Wilkins, L.: The Rates of Growth, Osseous Development, and Mental Development in Cretins as a Guide to Thyroid Treatment, J. Pediat. **12**:429, 1938.

Each animal was approximately one year of age. Distribution and biological decay of the labelled thyroxine in these animals was then studied over a 144-hour period, during which time blood samples were drawn at 3, 8, 24, 48, 72, 96, 120, and 144 hours, respectively. Red-blood-cell and plasma samples were counted, and an aliquot of the latter was subjected to normal-butanol extraction with resultant fractions accordingly being counted. During the study the animals were maintained in metabolic cages for separate urine and stool collection at cited intervals. Data thus obtained are presented in the Table.

As shown in the Table, I^{131} thyroxine counts (nonred blood cell diffusible or normal-butanol extractable) in plasma were high and consistently represented the predominant source of plasma counts present. During the study, thyroxine counts

I^{131}-Labelled Thyroxine Data in Macaque Monkeys

Animal*	Time, Hr.	Thyroxine Available, Cts./Sec.†	Counts Excreted, Cts./Sec.‡	Blood Cts./Sec./Gm.		Plasma *n*-Butanol I^{131} Fractions (% Plasma Cts./Sec./Gm.)		
				Plasma	RBC	*n*-Butanol	NaOH	Residue
A	0	125,000	.....	...	....	....	...	...
E	0	135,000	.....	...	....	....	...	...
A	3	123,000	.....	374	47.5	90.5	6.3	3.3
E	3	133,000	.....	514	57.0	94.4	4.1	1.3
A	8	121,300	5,770	284	75.0	90.3	6.5	3.9
E	8	131,500	7,650	375	55.0	91.7	4.9	3.4
A	24	114,700	23,600	147	35.0	88.1	7.2	4.7
E	24	124,000	28,500	177	27.0	94.3	3.8	2.0
A	48	83,500	11,910	79	22.0	....	...	...
E	48	87,800	13,400	109	25.0	....	...	...
A	72	65,500	8,100	51	11.0	87.5	6.9	4.5
E	72	68,000	8,860	72	7.0	91.7	4.4	4.0
A	96	52,500	7,100	29	7.1	80.3	10.8	9.0
E	96	54,100	6,570	41	6.0	96.8	2.7	0.6
A	120	41,500	4,900	...	6.0	77.7	11.2	11.1
E	120	44,400	4,000	27	....	84.2	10.1	5.8
A	144	33,500	4,250	14.5	4.0	....	...	...
E	144	37,100	3,000	19	3.0	....	...	...

* A indicates athyroid macaque B-767; E indicates euthyroid macaque I-793.

† Corrections for physical decay and previous excretion have been made before each entry. Represents remaining counts available at the time indicated.

‡ The fraction of "counts available" excreted during the immediately preceding interval. Includes counts appearing in urine and stool. Stool counts did not exceed 2% of available counts at any time. It also includes correction in the euthyroid animal for the 30%/day thyroid uptake and binding of iodide made available by thyroxine degradation. The 24-hour I^{131} uptake before and after current studies in that animal was consistently 30%, and subsequent thyroid release was consistently less than 4%/day.

decreased at a rate which could not be accounted for by excretion and/or accumulation of nonthyroxine counts in the animals. The progressive decrease in plasma thyroxine counts was interpreted to represent increment of its volume of distribution during the period of study. The latter was calculated by dividing the thyroxine counts per gram of plasma into the total thyroxine counts contained in the animal at intervals indicated (Fig. 6). "Extracellular" volume represents the two-hour Na^{24} volume of distribution [10] and the plasma volume approximated from unreported studies of blood volume using Cr^{51}-tagged red blood cells. The rate of increment in volume of distribution after 24 hours had a half-life of approximately three days.

The reported volume of distribution of I^{131}-labelled thyroxine following its intravenous administration in one human cretin was not unlike that found in the present

study.[28] The total thyroxine counts from which we defined the volume of distribution at specific intervals had been adjusted for counts excreted and nonthyroxine or diffusible counts, and thus represented thyroxine counts actually remaining in the animals.

The rate of biological decay of the I^{131}-labelled thyroxine administered in the present study was calculated from interval determinations of I^{131}-thyroxine label counts appearing in excreta. From our previous investigations it was observed that following intravenous administration as carrier-free iodide, 94 to 96% of I^{131} appeared in the urine within 24 hours (excretion half-life of six hours). That was equally true in the athyroid and the thyroxine-blocked normal animal. It was,

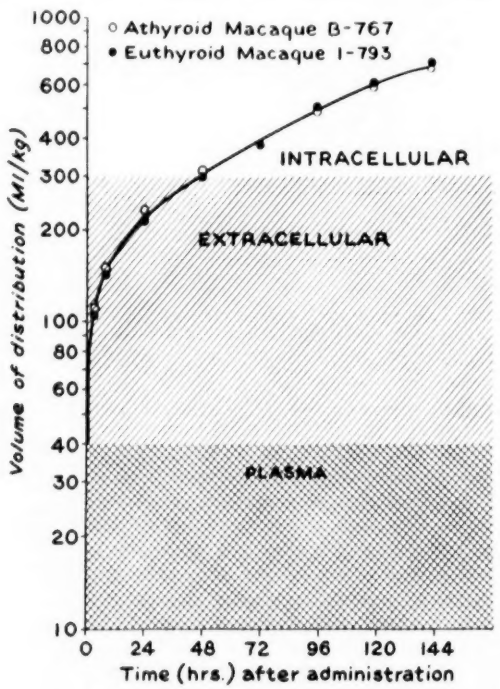


Fig. 6.—Distribution of I^{131}-tagged thyroxine following its administration.

therefore, assumed that the majority of counts made available through degradation of I^{131}-labelled thyroxine during any 24-hour period would appear in the excreta during that time. When so measured, the biological decay of I^{131}-labelled thyroxine was found constant with respect to rate and did not differ in the animals studied (Fig. 7).

Study A, Figure 7, relates the mentioned excretion pattern following the intravenous administration of I^{131} as carrier-free iodide, while Study B, Figure 7, pertains to the biological decay of I^{131}-labelled thyroxine administered. During

28. Albert, A., and Keating, F. R., Jr.: Metabolic Studies with I^{131} Labeled Thyroid Compounds: Comparison of the Distribution and Fate of Radioactive D-L-Thyroxine After Oral and Intravenous Administration in the Human, J. Clin. Endocrinol. **9**:1406, 1949

Study B, no more than 2% of counts excreted during any interval appeared in the stool of either animal. A comparable stool excretion was observed in the human study cited.[28]

It will be recalled that approximately 5% of counts contained in the initial I^{131}-labelled thyroxine preparation were as free iodide. For that reason, and in light of the rapid rate of free iodide excretion (Study A, Fig. 7), excretion counts as a measure of biological decay were postponed for a period of 24 hours following intravenous administration of the thyroxine preparation. Study B, Figure 7, describes the constancy in rate of appearance of label counts in excreta during each 24 hours of the 120-hour period of study, which began 24 hours following thyroxine

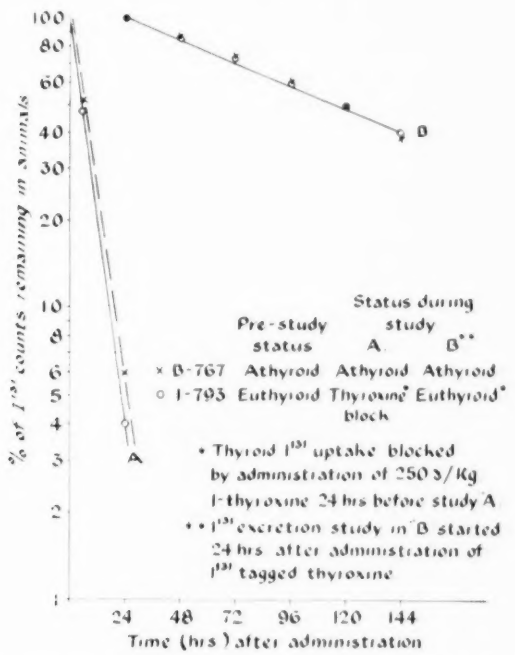


Fig. 7.—I^{131} excretion following intravenous administration of it as *A*, carrier-free iodine, or *B*, I^{131}-tagged thyroxine.

administration. During that time approximately 60% of thyroxine counts present in the animal at 24 hours appeared in excreta (more than 90% of which appeared in the urine). The biological decay half-life of thyroxine so calculated equalled 92 hours in each animal studied. It was approximately 25% slower than the half-life value for rate of tissue distribution.

One additional fact is implied by the observed uniformity in volume of distribution and biological decay of thyroxine, and would suggest that such processes are uninfluenced by either hormone concentration or the metabolic state of the host (euthyroid or athyroid). Hypothetically, a relative or actual thyroid hormone deficit in any organism could, therefore, be met only by increased thyroxine production and release by thyroid and a secondary increment in plasma and tissue

concentration. The increased metabolic demands of pregnancy seem to be met through such mechanisms, since it is known that during pregnancy the serum butyl-extractable iodine concentration in humans increased to the range of 7 to 10 γ per 100 cc. without coincident hyperthyroidism.[29]

The above studies with I^{131}-labelled thyroxine help to explain the observed differences in response of animals to optimal and suboptimal therapy with *l*-thyroxine. The relative slowness with which thyroxine assumes its ultimate volume of distribution can only be interpreted to mean that with suboptimal serum thyroxine levels, the skeleton does not receive sufficient hormone to meet its requirements.

It will be recalled that resumption of normal skeletal growth and maturation occurred singularly in those athyroid animals receiving 20 γ per kilogram per day and in whom serum butyl-extractable iodine concentration was maintained at a normal level, whereas animals receiving 6 γ per kilogram per day had serum butyl-extractable iodine levels of approximately 2 γ per 100 cc. and demonstrated a marked deficit with respect to skeletal growth and maturation.[30]

SUMMARY

Quantitative aspects of iodine metabolism were studied in six euthyroid and four athyroid immature macaque monkeys. Studies dealt with (*a*) factors relating to the uptake and organic binding of iodine by thyroid and (*b*) quantitative aspects relative to distribution, fate, and daily requirements of thyroxine in athyroid and euthyroid animals.

Twenty-four hour per cent I^{131} uptake by thyroid in normal animals decreased with age, being 35 to 45% in younger animals and dropping to 20 to 30% by one year.

Administration of thyroxine in quantities sufficient to produce greater than normal serum butyl-extractable iodine concentration effected suppression of thyrotropic hormone release by the pituitary.

Following its intravenous administration, 94 to 96% of carrier-free I^{131} was excreted within 24 hours in athyroid and normal animals whose thyroid uptake had been blocked by *l*-thyroxine administration.

Serum butyl-extractable iodine concentration in normal animals ranged from 4 to 8 γ per 100 cc., and, following I^{131} thyroid ablation, it dropped to less than 1 γ per 100 cc.

When studied over a 144-hour period following its intravenous administration to a normal and an athyroid animal, the volume of distribution of I^{131}-labelled thyroxine slowly assumed intracellular proportions.

The rate of biological decay of the I^{131}-labelled thyroxine administered had a half-life value of 92 hours in each animal.

M. Cole, M. Gaylord, and S. Hollingsworth assisted in this study.

29. Heinemann, M.; Johnson, C. E., and Man, E. B.: Serum Precipitable Iodine Concentrations During Pregnancy, J. Clin. Invest. **27**:91, 1948. Peters, J. P.; Man, E. B., and Heinemann, M.: Pregnancy and the Thyroid Gland, Yale J. Biol. & Med. **20**:449, 1948. Man, E. B.; Heinemann, M.; Johnson, C. E.; Leary, D. C., and Peters, J. P.: The Precipitable Iodine of Serum in Normal Pregnancy and Its Relation to Abortions, J. Clin. Invest. **30**:137, 1951.

30. Footnotes 1 *c*, *e*, and 2 *a*.

RELATIONSHIP OF ANESTHESIA TO POSTOPERATIVE PERSONALITY CHANGES IN CHILDREN

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SOME POSSIBLE deleterious effects of hospitalization and surgical operations on the personalities of children have been described.[1] However, apparently there has been no attempt to relate the experiences of the induction period of anesthesia to the development of undesirable personality changes afterward. It is difficult to establish precise relationships, because the experiences of hospitalization, anesthetization, and operation are not easily separated. A recent study of the effect preanesthetic medication has upon the course of anesthesia[2] has led to an investigation of possible relationship between anesthesia and personality changes.

Over an 18-month period, questionnaires were mailed to the parents of all children admitted to the Hospital of the University of Pennsylvania for an otolaryngological operation. Answers were sought to the following questions: 1. Is your child a bed-wetter; since operation does he wet the bed or wet it more frequently? 2. Does your child have night cries or terrors; since operation does he have night terrors or have them more frequently? 3. Is your child subject to temper tantrums; since operation do they occur or occur more frequently? 4. Has your child become afraid of meeting strangers since operation? 5. Has your child been afraid to have his face covered since operation? 6. Has your child become afraid of new odors since operation? 7. How did you prepare your child for hospitalization and operation?

Two months after the operation, letters containing the above questions were mailed to 1,008 parents. Replies were received from 612, or 61% of the total. Parents of children 12 years or older apparently were less interested in the study, since only 39% of this group replied. If this group is deleted from the study, the replies to the questionnaire would constitute 65%. Pertinent factors in groups answering or not replying appear to be homogenous in all respects, i. e., ward or private status, age, anesthetic agent employed, number of unsatisfactory inductions of anesthesia, and training status of the anesthetist. The results of the survey may be considered as truly representative for the entire group. The effects of preanesthetic medication upon the child scheduled for operation will not be considered here, since they have already been discussed.[2] In this study, preanesthetic medication

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1. (*a*) Coleman, L.: The Psychological Implications of Tonsillectomy, New York J. Med. **50**:1225-1228, 1950. (*b*) Levy, D. M.: Psychic Trauma of Operations in Children, Am. J. Dis. Child. **69**:7-25, 1945.

2. Eckenhoff, J. E.: An Analysis of the Effect of Preanesthetic Sedation in Children Operated upon for Tonsillectomy and Adenoidectomy, A. M. A. Arch. Otolaryng. **57**:411-416, 1953.

consisted of pentobarbital and scopolamine and usually morphine in dosage ranges recommended by Leigh and Belton.[3] Anesthesia was administered by resident or staff anesthetists, medical students, or interns under supervision. The anesthetist assigned had been asked to make detailed remarks concerning the condition of the child prior to induction and the course during induction and maintenance of anesthesia. Completed questionnaires were correlated with the anesthetic records of the children concerned.

RESULTS

Seventeen per cent of the replies indicated a personality alteration which might be traced to anesthesia and/or the hospital experience. Thirty-two per cent of the changes reported were in the form of night cries or terrors, appearing either for the first time or becoming worse after hospitalization. Temper tantrums comprised 26% of the changes; fear phenomena (afraid of darkness, unaccustomed odors, strangers, or of having face covered) constituted 23%; and the remainder (19%) pertained to bed-wetting.

Incidence of Postoperative Personality Changes in Children

	Age, Yr.									
% Changes	2	3	4	5	6	7	8	9	10	11+
50	..	..	..	..	..	..	..	..	..	..
	..	..	..	..	..	..	..	..	..	..
	..	..	..	..	..	..	..	..	..	..
40	X	X	..	..	..	..	..	..	..	..
	X	X	..	..	..	..	..	..	..	..
	X	X	..	..	..	..	..	..	..	..
30	X	X	..	..	..	..	..	..	..	..
	X	X	..	..	..	..	..	..	..	..
	X	X	X	..	..	X	..	..	..	..
20	X	X	X	..	..	X	..	..	..	..
	X	X	X	..	X	X	..	..	..	..
	X	X	X	X	X	X	X	..	X	..
10	X	X	X	X	X	X	X	..	X	..
	X	X	X	X	X	X	X	X	X	X
	X	X	X	X	X	X	X	X	X	X
0	..	..	..	..	..	..	..	..	..	..

The incidence of personality change was highest in the youngest children and was as clear-cut as in the report of Levy.[1b] The data are presented in the accompanying Table.

It can be seen that there was a relationship among age, reaction to the induction of anesthesia, and personality changes. With unsatisfactory inductions (crying, struggling, vomiting, and early obstruction), the probability of undesirable personality change was greater in young children than if induction were smooth. In relation to those inductions classified as being unsatisfactory, 57% of 3-year-olds had personality changes; 38% of 4-year-olds; 32% of 6-year-olds, and 14% of 8-year-olds. In children over the age of 8 years with unsatisfactory inductions, personality alterations averaged 8%, differing little from those of like age with satisfactory inductions. Reactions were surprisingly constant in the 3- to 8-year-olds with a smooth induction of anesthesia, the average incidence being 16% and the range 13 to 19%.

3. Leigh, M. D., and Belton, M. K.: Premedication in Infants and Children, Anesthesiology **7**:611-615, 1946.

The percentage of personality changes was approximately the same with all induction agents (cyclopropane, ethylchloride, and vinyl ether [Vinethene]), varying between 13 and 17%. A surprising finding, however, was that of 25 complaints related to bed-wetting, 23 were in patients given vinyl ether and only 2 with other agents.[4] On a percentage basis, bed-wetting was five times more common after administration of vinyl ether for induction of anesthesia. This finding is all the more interesting since there was no remarkable difference in other changes compared to the anesthetic agent administered.

In nine children, an incidental finding was that of convulsions or convulsive movements occurring during induction of anesthesia. Convulsions were seen in eight patients receiving vinyl ether or in whom a change to ethyl ether from vinyl ether had just been made. The ninth child was one subject to epileptic convulsions and in whom operation had twice been cancelled in other hospitals because of seizures occurring during the induction phase of anesthesia. On the third occasion (included in this series) anesthesia was induced with cyclopropane; a convulsion occurred two minutes after induction and lasted 45 seconds. The operation was completed without further incident. Vinyl ether was administered to 608 patients, and ethyl chloride, cyclopropane-nitrous oxide, or thiopental to the remaining 400.

The following are examples of statements found on returned questionnaires. The first three relate to preanesthetic medication.

CASE 1. (H. D., age 4 years, tonsillectomy).—"My only cause for complaint was that his sedative was not given to him soon enough before he was taken to the operating room, and the child was terrified."

CASE 2. (H. S., age 5 years, tonsillectomy).—"Due to the excellent way in which the operation was handled, my child has nothing but a pleasant recollection of his operation. I feel that was entirely due to the drug that was given him before he went to the operating room. My other child was given nothing before the ether, and was taken on an adult stretcher, and as a result is scared to death of hospitals. I firmly believe that if all children were given some drug to quiet them and make them good and drowsy, they would accept the anesthetic more readily."

CASE 3. (L. C., age 4 years, dilatation for posterior choanal atresia).—"I have noticed changes in her play. Everything is an operating room table, and she is always operating and giving needles to her dolls, her brothers, sisters and playmates. She is always pretending that she is giving ether, and I have to hide my needles or she is taking them and sticking everyone. My daughter knew what an operation meant, as she had had three operations on her elbow in the past 2 years, and two on her nose in 2 months. When it came time for her operation on her nose, we explained what was to be done and that afterward she might have a tube up her nose, but that the operation was to make her breathe normally again. I told her I would be there when she went to the operating room. She was very good and very interested in each phase of being prepared at the hospital.

"The first operation was in September and everything went smoothly. She was asleep when they took her to surgery. In the second operation which occurred in November, she was not medicated until about 5 minutes before they took her to surgery, and she left screaming in terror which I know was bad for her emotionally. It left a definite mark on her afterwards. She was afraid and did not want anyone to touch her afterward, and I even had trouble for awhile changing her tube at home. She would go into screaming tantrums. The first time she did just beautifully, and I had no trouble with her at home.

"My daughter may need another operation on her nose soon again, and before I allow it, I am going to make it understood with my doctor that she is to be medicated in time beforehand. . . ."

4. Agents employed for induction of anesthesia in the 612 patients were as follows: vinyl ether-ethyl ether, 363; nitrous oxide and/or cyclopropane-ethyl ether, 138; ethyl chloride ethyl ether, 101; thiopental-nitrous oxide or thiopental-ethyl ether, 10.

A fourth case concerns the importance of relationships between anesthetist and patient.

CASE 4. (G. H., age 6 years, tonsillectomy).—"He was quite brave about the whole thing and the only thing he ever mentions about his trip to the hospital is the praise he received from the doctor when he blew up the balloon. I imagine this occurred when he was getting the ether, but he keeps telling us how the doctor told him that he was one of the best youngsters he ever saw at blowing up the balloon."

The final two cases are indicative of lack of proper preparation for the experience of hospitalization and operation.

CASE 5. (B. O., age 4 years, tonsillectomy).—"I told her she was going to the hospital to see the newborn babies. After she was in the hospital she was told the truth."

The postoperative personality changes consisted of increased frequency of night terrors and temper tantrums and fear of strangers.

CASE 6. (G. F., age 3 years, tonsillectomy).—"When I took her to get her tonsils out, I told her she was going to play with all the little girls and see the babies. She thought that was wonderful. Since the operation she just cries all the time and is a very restless sleeper and cries in her sleep. I want to bring her back for a check-up on her nerves, but just can't do it because she screams and carries on high and says, 'Don't leave me there Mommie.' She thinks right away they are going to keep her. . . ."

COMMENT

One cannot blame all personality defects or abnormalities on unfortunate experiences with hospitals. However, this and other studies suggest that such experiences may be important. The better the child's home preparation for his experience of hospitalization and operation, the lower should be the incidence of postoperative personality changes. Many doctors do not advise parents as to how best to prepare children. Adults view these matters through their own eyes, forgetting the child's outlook and making little effort at preparations. Some parents apparently believe that the best way to handle the situation is to tell falsehoods. On a few occasions in the operating room, we have been confronted by children demanding the ice cream promised to be awaiting them.

Our experience indicates that it is important for physicians to advise parents about psychological preparation of the child. Helpful suggestions may be written with other preoperative instructions so that parents can refer to something rather than rely on memory. In the returned questionnaires, there were some descriptions of excellent preoperative preparation, but too few to allow correlation between preparation and personality changes. It would indicate, however, that with the proper stimulus from the physician, the number of adequate preparations could be increased.

A previous report has demonstrated a clear-cut relationship between the type of preanesthetic medication and the incidence of crying prior to induction of anesthesia. It was shown that 35 to 40% of children 5 years of age or less who received only atropine or scopolamine cried. Induction of anesthesia was always classified as unsatisfactory under those circumstances. It was further shown that the use of a barbiturate with the belladonna drug, plus careful attention to the time of administration of the drugs, significantly reduced the incidence of crying. In this respect it was reasoned that the crying child might be the one in whom personality changes were most likely to develop. The data presented herein indicate such reasoning was correct. Careful attention to preanesthetic medication could materially reduce undesirable sequelae. It is of interest, nevertheless, that in 16% of young children with

satisfactory induction of anesthesia personality changes developed. Presumably, the numbers in this group could be reduced by more attention to home preparation, efforts at improved relationships between hospital personnel, parents, doctors, and patient, and possibly more careful attention to preanesthetic medication. Obviously, skill of administration of anesthetics remains of prime importance. Some children had satisfactory inductions of anesthesia, but their medication had been given too late or too early. It is possible that suppressed fears could have resulted in subsequent personality conflicts, even though the children appeared cooperative, and induction was smooth.

The clinical impression has been expressed that vinyl ether anesthesia is associated with a higher incidence of bed-wetting and appearance of undesirable personality changes. We could establish no unusual relationships for the latter, but the association with bed-wetting was obvious and striking. The explanation for this response is not apparent.

The incidental observation that eight anesthetic convulsions occurred in 621 anesthesias where vinyl ether was used for induction closely parallels the data of the previous report,[2] wherein there were nine convulsions in 674 anesthesias during which vinyl ether was employed. The phenomena of muscular activity with vinyl ether has been reported in animals, but the explanation is not clear. These convulsions all responded to ventilation of the lungs with oxygen, though cyanosis before the convulsions was not always detectable. However, the latter does not rule out anoxia as having been present. If one were to assume that oxygen lack were the prime factor, the incidence of convulsions should have been the same with all agents. Because of the response to oxygen it may be advisable always to give oxygen simultaneously with vinyl ether. This matter is now being investigated.

From the foregoing two paragraphs, one cannot help but speculate on the significance of vinyl ether being associated with a high incidence of enuresis and with convulsions occurring more commonly than with any other anesthetic agent studied. This warrants further consideration.

The results of this investigation have stimulated interest for a thorough study of the problem. Obviously, a questionnaire survey is inferior to interviewing parents and direct observation of children before and after anesthesia. This report is therefore submitted as a compilation of preliminary observations. An attempt will be made to begin a long-term study utilizing the services of social workers and psychiatrists, as well as anesthetists. Likewise, the investigation will be broadened to include children for all types of surgery and not those for otolaryngological operations only.

SUMMARY

The results are presented of an investigation correlating the preparation and induction of anesthesia with personality changes in 612 children who underwent otolaryngological operations. It has been observed that 17% of the children had personality changes that might be attributed in part to inadequate preanesthetic or anesthetic management; that the younger the child, the more likely the development of personality changes; that unsatisfactory preanesthetic medication and induction of anesthesia is associated with a high incidence of personality changes in young children, and that bed wetting occurs five times more commonly after the use of vinyl ether (Vinethene) than after other techniques.

Miss Angela Verratti, R.N., assisted in obtaining the material for this report.

PINWORM INFECTION (ENTEROBIASIS) IN CHILDREN

A Comparative Study of Four Oxyuricides

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THE HIGH incidence of pinworm infection, in both children and adults, has been reported from all parts of the world. It is estimated that there are 209,000,000 cases of pinworm infection throughout the world.[1] The incidence among school children varies considerably in different areas. Stoll and co-workers [2] reported the lowest incidence, 1%, in Guam school children. Sutliff and Echandi [3] reported an incidence of 4.3% in hospitalized children in San Jose, Costa Rica. Killingsworth and co-workers [4] reported an incidence of 32% in Port Arthur and Houston, Texas. Askue (personal communication) reports an incidence of 30% in clinic and hospitalized children in Philadelphia. Kuitunen-Ekbaum [5] reported an incidence of 60% in Toronto, Canada, children. Cristovao [6] in a study of 309 children in Sao Paulo, Brazil, found 60% infected. Voplenko [7] in a study of 6,552 Russian children reported a low incidence of 17%. The incidence reported from Mexico City children varies from 41% to as high as 95%.[8] In a study of 1,000 children in Amsterdam,

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1. Stoll, N. R.: This Wormy World, J. Parasitol. **33**:1-18 (Feb.) 1947.

2. Stoll, N. R.; Chenoweth, B. M., Jr., and Peck, J. L., Jr.: Low Incidence of Enterobius Vermicularis in Natives of Guam, M. I., Puerto Rico J. Pub. Health & Trop. Med. **22**:235-243 (March) 1947.

3. Sutliff, W. D., and Echandi, G. R. A.: Pinworm (E. Vermicularis) and Other Intestinal Parasites in Costa Rican Children, J. Parasitol. **32**:233-236 (June) 1946.

4. Killingsworth, W. P.; Meyer, P. R.; McFadden, I. M., and Boardman, H. L.: Treatment of Pinworms (Oxyuriasis): Clinical Evaluation Based on 1,005 Cases, Texas J. Med. **48**:27-31 (Jan.) 1952.

5. Kuitunen-Ekbaum, E.: Incidence of Enterobiasis in Toronto, Canad. M. A. J. **48**:229-231 (March) 1943.

6. Cristovao, D. de A.: Do valor do metodo do "swab" N. I. H. no diagnostico da enterobiose intestinal e da incidencia desta em crianças de São Paulo, Rev. clin. São Paulo **9**:148-160 (May) 1941.

7. Voplenko, V. V.: Incidence of Helminths in Young Children in Baku, Med. Parasit., Moscow **12**:83 (Dec.) 1943.

8. Mazzotti, L., and Quintanar,, E.: (a) La importancia de los examenes repetidos en el diagnóstico de la oxiuriasis, Rev. Inst. salub. y enferm. trop. **4**:167-171 (June) 1943. (b) Examen de 1,551 niños de la ciudad de Mexico, utilizando el método de Graham, para investigar oxiuriasis, Rev. Inst. salub. y enferm. trop. **4**:173-178 (June) 1943.

Hummelen [9] reported an infection rate of 85%, while Schüffner [10] reported a 100% incidence in Amsterdam children. Jirovec [11] reported an incidence of 80% in 2,500 children studied in Bohemia. Cram [12] reported an incidence of 41.5% in white children in the District of Columbia and 12.9% in Negro children. This rather marked difference in incidence between Negro and white children has also been observed by the authors and many other investigators. In a study of 1,145 children at the Edward J. Meyer Memorial Hospital in Buffalo, 20% were infected. In this study the incidence was highest in the toddler and elementary school age group. The youngest infected child was an 18-month-old patient. The youngest reported case of pinworm infection was a 5-week-old infant reported by Killingsworth.[4] The lowest infection rates reported in the literature are among adults and Negroes. The high per cent of Negroes in our study (52%) in part explains the relatively low incidence in our hospital study.

Another interesting observation that we have made on the incidence of enterobiasis is the absence of pinworm infection in our pediatric tuberculosis patients. Of 34 children infected with various types of tuberculosis none were infected with pinworms. However, 21 of these children were Negroes and only 13 were white. Only seven of these children were on antibiotic or chemotherapeutic regimens. The remainder were on the usual tuberculosis regimen.

CLINICAL IMPORTANCE

Sufficient evidence exists, judging from the statements made by many mothers in our private offices and hospital clinics, that many physicians view the pinworm infection problem with indifference and impress parents that pinworm infections are unimportant and only of nuisance value. While the symptoms caused by pinworm infection are most usually mild and occasionally absent, about 25% of infected children have symptoms severe enough to warrant definite diagnosis and treatment. Severe morbidity and even death due to pinworm infection have been reported. Bijlmer,[13] in 1946, reported a fatal case of pinworm invasion of the intestinal wall. Miller,[14] in 1948, reported a chronic inflammatory intestinal obstruction due to Enterobius vermicularis, and Deeds,[15] in 1947, reported a case of pinworm migration to a round ligament lymph node. Many reports appear in the literature on the possible causal relationship between appendicitis in children and pinworm infec-

9. Hummelen, L. R.: Helminthiasis in Children, Particularly in School Medical Officer's District in Huizen, Thesis for Doctorate, Amsterdam, 1945; abstracted, Trop. Dis. Bull **43**:355 (April) 1946.

10. Schüffner, W.: Eine verbesserte Methode des Nachweises von Enterobius (Oxyuris) Eiern, Klin. Wchnschr. **22**:521 (Aug. 7) 1944.

11. Jirovec, O., and Rozehnal, V.: A New Treatment of Oxyuriasis with a Combination of Phenothiazine, Hexylresorcinal and Basic Fuchsin, Prakt. lék. 355-357, 1950.

12. Cram, E. B., and Reardon, L.: Studies on Oxyuriasis: Epidemiological Findings in Washington, D. C., Am. J. Hyg. (Sect. D) **29**:17-24 (Jan.) 1939.

13. Bijlmer, J.: Exceptional Case of Oxyuriasis of Intestinal Wall, J. Parasitol. **32**:359-366 (Aug.) 1946.

14. Miller, J. M., and Ginsberg, M.: Chronic Inflammatory Intestinal Obstruction Due to Enterobius Vermicularis, Surgery **24**:57-61 (July) 1948.

15. Deeds, D. D.: Migration of Oxyuris Vermicularis to Lymph Node of Round Ligament, Am. J. Obst. & Gynec. **54**:890-892 (Nov.) 1947.

tions.[16] It is estimated that in 5 to 10% of all cases of appendicitis in children, sufficient worms are found in the appendix to establish a definite relationship between appendicitis and pinworm infection.

SYMPTOMS

The symptom which is present, in varying degrees of intensity, in almost all cases of pinworm infection is pruritus ani, especially nocturnal. With the pruritus ani, most usually, the anal orifice is excoriated and a ring of erythema and excoriation the size of a 25- or 50-cent piece surrounds the anal orifice. Disturbed sleep and restlessness at night together with nocturnal enuresis and irritability with fatigue during the day are also usually seen in heavily infected children. Other symptoms frequently seen are pruritus vulvae, with nonspecific vaginitis, vague abdominal pain and discomfort, anorexia, inattention in school with resulting poor school performance, and various disturbed behavior attitudes. We are sufficiently impressed with the improved general attitude and behavior of the infected children after they are successfully treated to recommend that all children with disturbed sleeping and eating patterns and classroom problems, social or scholarship, as well as all children with anal orifice excoriation accompanied with pruritus ani and all cases of vaginitis in female children should have enterobiasis diagnostic Scotch-tape tests.

DIAGNOSIS

The diagnosis of pinworm infection is a simple office procedure. Any one of the newer simplified anal swab techniques can be used to establish the diagnosis.[17] The method we used in our study was a modification of the Graham Scotch-tape-swab technique. A piece of ordinary Scotch tape ½ in. (1.3 cm.) wide and about 3 in. (7.6 cm.) long was looped over the end of a tongue depressor, with the adhesive surface on the outside. The ends of the Scotch tape were held firmly by thumb and index fingers against the tongue depressor. The adhesive surface of the Scotch tape was then touched to the anal orifice, making sure that both sides of the perianal surfaces were contacted by the Scotch tape. Then the Scotch tape was firmly pressed, lengthwise, on an ordinary microscope slide with the adhesive surface against the slide and without preparation was examined under the 16-mm. microscope objective. With this technique the microscopic eggs, which are ovoid and asymmetrical, measuring 55 by 26 μ and containing the coiled-up embryo, can be readily identified. The presence of eggs definitely establishes the diagnosis of enterobiasis. If a drop of toluene or xylene (xylol) is first placed on the glass slide and the Scotch tape then pressed on the slide over the drop of the toluene or xylene, the extraneous matter under the Scotch tape is dissolved, and the pinworm eggs stand out more

16. Ashburn, L. L.: Appendiceal Oxyuriasis: Its Incidence and Relationship to Appendicitis, Am. J. Path. **17**:841-856 (Nov.) 1941. Velkoff, C. L.: Correlation of Appendicitis and Oxyuris Vermicularis, Virginia M. Month. **77**:75-76 (Feb.) 1950. Gordon, H.: Appendiceal Oxyuriasis: Study of Its Incidence in 20,969 Extirpated Appendices, Ann. Int. Med. **4**:1521-1534 (June) 1931.

17. Hall, M. C.: Studies on Oxyuriasis: Types of Anal Swabs and Scrapers, with Description of Improved Type of Swab, Am. J. Trop. Med. **17**:445-453 (May) 1937. Graham, C. F.: Device for Diagnosis of Enterobius Infection, ibid. **21**:159-161 (Jan.) 1941. Von Hofe, F. H.: Improved Method of Demonstrating Ova of Enterobius Vermicularis, J. A. M. A. **125**:27 (May 6) 1944. Markey, R. L.: Anal Swab Method for Detection of Enterobius Vermicularis, Am. J. Clin. Path. **20**:493-494 (May) 1950.

vividly, thus making identification easy even for the inexperienced examiner. Frequently, with this simple preparation of the Scotch tape smear a very feeble but definite activity of the embryonic form inside the egg shell can be visualized. The optimal time to take the diagnostic smears is early in the morning before the child is cleansed and bathed. The technique of taking the smears is simple enough so that the mother can do this at home when the child arises in the morning. We have found that considerable time and expense can be saved if smears are taken on the entire family, father included, at the same time and if the entire family, father included, is treated simultaneously, even if only one member of the family has a positive diagnostic smear.

The mother frequently can identify the adult female worm, which is about ¼ in. (0.6 cm.) long and as thick as a silk thread, white and motile, in the perianal area, usually seen emerging from the anal orifice and occasionally from the vagina in the female child. If the mother's description is sufficiently accurate a definite diagnosis of enterobiasis can be made in the presence of the usual symptoms and the clinical suspicion of the pinworm infection.

Examination of stools for diagnosis is not only a tedious laboratory procedure but also time-consuming, expensive, and unnecessary. Even though the mother identifies the adult female worm in the stool, by the time the stool is brought to the laboratory or the doctor's office for examination the female worm oviposits and disintegrates so that no worm can be found in the stool, excepting in cases of very heavy infection. The male worm rarely if ever is seen in the stool because the male disintegrates shortly after mating.[18] Many investigators have reported that the percentage of positive diagnoses made by the anal-swab technique is five to eight times greater than by the stool-examination technique.[19]

In a study of 240 children Headlee [20] found no correlation between the eosinophile count of the peripheral blood smear and the presence or absence of pinworm infection. This observation has been confirmed in our study of hospital patients who were infected with pinworms.

MODE OF INFECTION

A knowledge of the simple life cycle of the E. vermicularis as outlined below will make the transmission of infection clear.

1. Microscopic eggs (55 by 26 μ) are swallowed by the human host.
2. Intestinal juices stimulate hatching into young male and female oxyurides.
3. These grow rapidly to sexual maturity and mate in the lower small intestine and ceacum.
4. After mating the male dies and disintegrates.
5. The fertilized female reaches the colon and emerges from the anus after the host has gone to bed.
6. The cooler temperature outside the anus causes violent contraction of the female.

18. Belding, D. L.: Textbook of Clinical Parasitology Including Laboratory Identification and Technic, New York, Appleton-Century-Crofts, Company, Inc., 1942.

19. Sawitz, W.; Odom, V., and Lincicome, D. R.: Diagnosis of Oxyuriasis: Comparative Efficiency of NIH Swab Examination and Stool Examination by Brine and Zinc Sulfate Floatation for Enterobius Vermicularis Infection, Pub. Health Rep. **54**:1148-1158 (June) 1939. Hummelen.[9]

20. Headlee, W. H.: Pinworm Infections Among Patients of an Indiana Hospital for Children, Am. J. Trop. Med. **23**:281-284 (March) 1943.

7. The female bursts and oviposits 10,000 to 15,000 fertilized eggs in the perianal folds.
8. Scratching fingers transfer fertilized eggs to the mouth.
9. The life cycle starts again (Complete life cycle varies from 10 days to 2 months).[21]

The E. vermicularis is exclusively a human parasite. The life cycle is completed only in the human host, and even though household pets are frequently accused of being the source of pinworm infection, attempts to infect experimental animals have been unsuccessful.[21e]

The microscopic pinworm eggs not only contaminate household furnishings, toys, and clothing, but, since they are light enough to float in the air, they can be inhaled into the upper respiratory tract and then swallowed into the esophagus or can be coughed up after inhaled into the lungs and then swallowed into the gastrointestinal tract. This physical characteristic of the eggs, coupled with their resistive three-layer shell, a protein outer layer, a double chitin layer, and an inner sterol layer, makes the eggs resistive to most antiseptic solutions and makes the prevention of pinworm infection a most formidable problem.

TREATMENT

Since the first recorded[22] treatment for pinworms, in 1701, many drugs have been used by mouth, in enemas, and in topical applications. Table 1 records the percentage of cures obtained by various investigators,[23] with the most widely used oxyuricides.

Other drugs which have been used to a lesser extent are hexylresorcinal orally, Lubisan (resorcinol derivative) Acranil (acridine dye) quinacrine (Atabrine), diphenhydramine (Benadryl), piperazine, santonin, and quassia chips. Because of toxicity or questionable efficiency these drugs have not been used widely or have been discarded as ineffective oxyuricides. Toxic effects have also been reported with hexylresorcinal by mouth and in enemas [4] and also with phenothiazine [23d] orally.

21. (*a*) Brady, F. J.: Pinworm Infection and Trichinosis, Am. Pract. **1**:583-588 (July) 1947. (*b*) Brady, F. J., and Wright, W. H.: Studies on Oxyuriasis: Symptomatology of Oxyuriasis as Based on Physical Examination and Case Histories of 200 Patients, Am. J. M. Sc. **198**:367-372 (Sept.) 1939. (*c*) Cram, E. B.: Studies on Oxyuriasis, Summary and Conclusions, Am. J. Dis. Child. **65**:46-59 (Jan.) 1943. (*d*) Faust, E. C., and Brennemann, J.: Practice of Pediatrics, Hagerstown, Md., W. F. Prior Company, Inc., 1944, Vol. 2, Chap. 35, p. 8. (*e*) Jones, M. F., and Jacobs, L.: Studies on Oxyuriasis: Survival of Eggs of Enterobius Vermicularis Under Known Conditions of Temperature and Humidity, Am. J. Hyg. (Sect. D) **33**:88-102 (May) 1941.

22. Andry, N.: De la generation des vers dans le corps de l'homme, Amsterdam, 1701, p. 167.

23. (*a*) D'Antoni, J. S., and Sawitz, W.: Treatment of Oxyuriasis, Am. J. Trop. Med. **20**:377-383 (May) 1940. (*b*) Miller, M. J., and others: Studies on Pinworm Infection: Tests with Gentian Violet in Treatment of Pinworm Infection, Canad. M. A. J. **43**:455-458 (Nov.) 1940. (*c*) Footnote 4. (*d*) Miller, M. J., and Allen, D.: Studies on pinworm Infections: Tests with Phenothiazine in Treatment of Pinworm Infections, Canad M. A. J. **46**:111-115 (Feb.) 1942. (*e*) Kuitunen-Ekbaum, E.: Phenothiazine in Treatment of Enterobiasis, Canad. Pub. Health J. **32**:308-313 (June) 1941. (*f*) Goddard, R. F., and Brown, H. W.: The Treatment of Pinworm Infection (Enterobius Vermicularis) with Egressin, J. Pediat. **40**:469-473 (April) 1952. (*g*) Miller, M. J., and Choquette, L. P. E.: Studies in Pinworm Infections: Tests with p-Benzylphenyl Carbamate in Treatment of Pinworm Infections, Canad. M. A. J. **62**:271-274 (March) 1950. (*h*) Loughlin, E. H., and others: The Treatment of Enterobiasis with Terramycin Base, Antibiotics & Chemother. **1**:588-593 (Dec.) 1951.

In addition to the toxic effects of some medicated enemas, enemas even of plain water or nontoxic medications have many decided disadvantages. Enemas given nightly, especially in large families, become a discouraging chore that tires the mother both physically and emotionally. We infrequently and reluctantly recommend enemas in the treatment of enterobiasis, and then only when we recognize a mother that has the needed physical and emotional stamina or to mothers of one- or two-children families. However, in our experience, we have found that the children that have the heaviest worm burden are the children in the large families.

The physical structure of pinworm eggs makes them resistive to the usual antiseptic ointments that have been used topically in the treatment of enterobiasis. These ointments serve to relieve the pruritus and perhaps also help to trap the eggs and worms at the anal orifice until the child is bathed. It is thus possible that the local use of antiseptic or antipruritic ointment can help to keep the egg concentration

TABLE 1.—*Percentage of Cures Obtained by Various Investigators*

Therapeutic Agent	% Cured	Investigator
Methylrosaniline (gentian violet) orally	90	D'Antoni and Sawitz [23a]
Methylrosaniline orally	90	Miller and co-workers [23b]
Methylrosaniline orally and hexylresorcinol enema	56	Killingsworth and co-workers [23c]
Methylrosaniline orally	60	Miller and Allen [23d]
Methylrosaniline orally	82	Bumbalo and co-workers
Phenothiazine orally	64	Miller and Allen [23d]
Phenothiazine orally	86	Kultumen-Ekbaum [23e]
Egressin (thymyl-n-isoamylcarbarmate) orally	52	Bumbalo and co-workers
Egressin orally	40	Goddard and Brown [23f]
Diphenan (p-benzylphenylcarbamate) orally	8.8	Miller and Choquette [23g]
Diphenan orally and hexylresorcinol enemas	77	Killingsworth [4]
Diphenan orally	30	Bumbalo and co-workers
Oxytetracycline (Terramycin) base (orally)	97	Loughlin and co-workers [23h]
Oxytetracycline (orally)	81	Bumbalo and co-workers
Garlic (raw or deodorized) orally	87	Killingsworth and co-workers [23c]
Pyribenzamine (tripelennamine) hydrochloride orally and hexylresorcinol enema	56	Killingsworth and co-workers [23c]
Hexylresorcinol enemas	36	Killingsworth and co-workers [23c]
Tetrachloroethylene	20	Killingsworth and co-workers [23c]

of the contaminated air in the infected child's room to a minimum. Egg concentration is also reduced in hot dry air. Boardman [4] suggested superheating sleeping rooms to 134 F. daily as part of the pinworm treatment. We are of the opinion that this routine is not practical enough for the average family living in the average home.

CLINICAL EVALUATION OF FOUR OXYURICIDES

In the past year we have treated patients in a series of 160 cases of enterobiasis at the Edward J. Meyer Memorial Hospital. Forty-two per cent were hospitalized patients and 58% were clinic patients. None of these patients were being given any medication, by any route, that had been used as an oxyuricide, except the specific oxyuricide used in the study of these patients. The patients were divided into four groups, each totaling 40. The patients in Group I were treated with Egressin (thymol-*n*-isoamylcarbamate) by mouth, in Group II, with Diphenan (parabenzylphenylcarbamate) by mouth, in Group III, with methylrosaniline (gentian violet enseal tablets) by mouth, and in Group IV, with oxytetracycline (Terramycin) by mouth.

The diagnosis in all of these patients was established by the Scotch-tape-swab technique described in this report in the section discussing diagnosis. Seven days after cessation of treatment all patients were checked by daily Scotch-tape-swab smears to determine the results of the treatment. Only those patients who had seven consecutive negative smears were declared cured. Those patients who had a positive smear, even on the seventh day, were declared failures and are not reported in this study. Table 2 lists the number of patients treated with the various drugs, the dosage used, the duration of treatment, and the results.

In addition to the drug therapy all patients were instructed to carry out strict personal and environmental hygiene as indicated below.

1. Keep fingers and playthings out of mouth
2. Keep nails cut short
3. Scrub hands and nails after toilet and before meals
4. Bathe each morning, shower preferred
5. Clean personal linen and bedding daily, if possible
6. Separate wash cloth and towel for face and body

TABLE 2.—*Treatment and Results*

Drug	Patients	Dosage	Duration, Days	% Cured
Eggressin (thymol-*n*-isoamylcarbamate)	40	0.87 gm./lb. body weight divided in 3 daily doses p. c.	5 only	52
Diphenan (*p*-benzylphenyl-carbamate)	40	Up to 5 yr. ½ wafer t. i. d. 5-12 years 1½ wafers t. i. d. 12 years up, 2 wafers t. i. d.	8 only 8 only 8 only	30
Methylrosaniline (gentian violet)	40	1 mg./lb. body weight divided into 3 daily doses 1 hr. a. c.	8 days 7, rest 8 repeat	82
Oxytetracycline (Terramycin)	40	10 mg./lb. body weight divided into 3 daily doses p. c.	7 only	84

7. Sterilize nonwashable toys
8. Vacuum clean bedroom daily
9. Raise room temperature as much as possible each morning for two hours and then air
10. Apply carbolated petrolatum to perianal area

An additional hygienic measure which was not carried out in this study but which is now being recommended as an hygienic measure is the soaking of bed linens and sleeping clothes in household ammonia. Killingsworth [4] has shown that soaking linens in household ammonia in a 1 : 160 (2 teacups [approximately 470 ml.] to 10 gal. [38 liters] of water) dilution at room temperature for one hour will destroy or devitalize pinworm eggs.

Egressin,[24] a new nontoxic and safe chemotherapeutic agent, while easy to administer and well tolerated, produced a relatively low percentage of cures. Using this new drug, Sauer and Weissflug [25] reported a cure rate of 95% as compared to our cure rate of 52% and to Goddard and Brown's cure rate of 40%. While the enterobicidal properties of Egressin, as observed to date, are not too striking, we are of the opinion that further treatment studies with increased dosages are indicated.

24. Egressin was provided by Sharpe and Dohme Co., Philadelphia.

25. Sauer, A., and Weissflug, I.: Klinische Prüfung des Egressin, Schweiz. med. Wchnschr. **80**:737-738 (July) 1950.

Diphenan [26] is also a nontoxic palatable and easy medication to administer to children. In our study the cure rate was even lower than with Egressin. Killingsworth and co-workers [4] used Diphenan by mouth for 14 days and after a pause of 7 days the drug was repeated for 14 more days. In addition to the Diphenan they gave hexylresorcinal enemas (2 tablespoonfuls of hexylresorcinal mixed with 4 oz. of warm tap water) every night at bedtime. With this combined treatment they reported a 77% cure rate. However, there are other reports in the literature [27] that report even smaller cure rates than we obtained with Diphenan. Because of the relatively low cure rate and high cost of the drug, in our opinion, Diphenan is not a satisfactory oxyuricide.

Methylrosaniline [28] cured 82% of our patients, but it too has some disadvantages. Many children, particularly the younger ones, are unable to swallow the intact tablets. While solutions of methylrosaniline have been used by some (personal communication) in our observations, solutions of methylrosaniline are very irritating and invariably cause nausea and vomiting. Occasionally in some children methylrosaniline causes abdominal cramps followed by nausea and vomiting. Even though the percentage of cures with methylrosaniline is higher than those obtained with Egressin and Diphenan, it too cannot be considered a completely satisfactory oxyuricide.

Oxytetracycline hydrochloride was first used in the treatment of pinworm infection by Wells and co-workers with considerable success, but this was not entirely devoid of unfavorable reactions.[29] Using the intermediate amphoteric form of oxytetracycline known as oxytetracycline base, 1 to 2 gm. daily for five days, Loughlin and co-workers [23b] reported 97% cures. In our study using oxytetracycline, base or hydrochloride, in doses of 10 mg. per pound (0.5 kg.) of body weight, daily, for seven days, we obtained 84% cures. The oxytetracycline was well tolerated and easy to administer in the drop form to the younger children and in the oral suspension or capsules to the older children. No gastric upset, diarrhea, or other evidence of toxicity was observed in all 40 cases.

While the exact action of oxytetracycline in the treatment of pinworm infection is not definitely determined, the work of Loughlin and co-workers suggests that oxytetracycline probably exerts some direct deleterious action upon the mature gravid female worms and also upon the fertilized eggs. These effects are manifested by the progressive alteration of the morphology of the eggs during the course of treatment with oxytetracycline.

While oxytetracycline [30] cured the greatest number of patients in this study, it too has disadvantages. Oxytetracycline is an antibiotic and as such we would like to caution that it should be used with some degree of discretion. The cost of oxytetracyclin, particularly when it is administered to all members of a large family, is perhaps its major drawback.

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26. Diphenan was provided by the Burroughs Wellcome & Co., Inc., Tuckahoe, N. Y.

27. Footnote 23*a*. Kuitunen-Ekbaum, E., and James, D. M.: Diphenan in the Treatment of Enterobiasis, Canad. J. Pub. Health **41**:167-169 (April) 1950.

28. Methylbrosaniline (gentian violet) was provided by Eli Lilly & Co., Indianapolis.

29. Wells, H. A. S., and others: Terramycin HCl in the Treatment of Human Pinworm Infections, Antibiotics & Chemother. **1**:299-304 (Aug.) 1951.

30. Oxytetracycline (Terramycin) was provided by the Chas. Pfizer & Co., Brooklyn, N. Y.

SUMMARY

The incidence of pinworm infection is higher than is commonly suspected. Incidence reports from different parts of the world vary from 1% in Guam to 100% in Amsterdam children. The incidence in white children is about four times greater than in Negro children. In this study 34 children on our pediatric tuberculosis service were repeatedly found to be free of pinworm infection.

Pinworm infection is a public health and economic problem that warrants a greater interest from physicians and investigators.

The symptomatology of pinworm infection can occasionally be absent but most usually is manifest by pruritus ani, excoriation of the anal orifice and anocutaneous area, restlessness, and vaginitis.

The diagnosis of enterobiasis is a simple procedure. A modification of the Graham Scotch-tape-swab technique was used in this study and is described in detail. The examination of stools to establish the diagnosis of pinworms is unnecessary, time-consuming, and costly. In this study we have confirmed a reported observation that an increase in the eosinophiles of the peripheral blood smear is not observed in enterobiasis.

The life cycle of the Enterobius vermicularis and the characteristics of pinworm eggs are described. Infection with the E. vermicularis is seen in man only and is transmitted from person to person by the ingestion of the fertilized eggs which can become gravid females, ovipositing 10,000 to 15,000 eggs ready to start a new life cycle in 14 to 60 days.

Four oxyuricides, two of them Egressin and oxytetracycline (Terramycin), comparatively new, were studied in the treatment of 160 children infected with pinworms. Four groups, each comprised of 40 patients, were treated with Egressin, Diphenan, methylrosaniline (gentian violet), and oxytetracycline. Egressin was effective in 52%, Diphenan in 30%, methylrosaniline in 82%, and oxytetracycline in 84% of the patients treated. In addition to the drug therapy, strict personal and environmental hygienic measures were carried out.

All four of the oxyuricides studied have some advantages and some disadvantages. Oxytetracycline was the most effective drug, but the cost of the drug in treating families is a decided drawback. We are of the opinion that the ideal oxyuricide has not yet been found. The drug that will be the most satisfactory oxyuricide must be completely harmless, easy to take, well tolerated and inexpensive, so that large groups can be treated simultaneously to avoid the possibility of reinfection.

Case Reports

BILATERAL OPTIC NEURITIS FOLLOWING SMALLPOX VACCINATION AND DIPHTHERIA-TETANUS TOXOID

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OPTIC NEURITIS accompanying encephalitis is a rare but well-established complication of smallpox and antirabic vaccination.[1] Optic neuritis without central symptoms is, however, an extremely rare complication of immunization procedures. Duke-Elder,[2] noting the reports of Cormack and Anderson [3] and Hasabe,[4] states that "a severe neuritis without necessarily other central symptoms but involving abolition of light may follow an *antirabic inoculation*." In 1949, Ross [5] decribed one case and Siegert [6] three cases of bilateral optic neuritis following the administration of diphtheria toxoid. Following is the report of a case of bilateral optic neuritis which followed simultaneous smallpox vaccination and combined diphtheria-tetanus toxoid administration.

REPORT OF CASE

A 7-year-old white girl was brought to the hospital on May 13, 1952, complaining of a sudden decrease in visual acuity of three days' duration. She had no other complaints, and her parents had noted no symptoms of any illness. Further questioning disclosed that two weeks previously she had received a booster dose of alum-precipitated combined diphtheria-tetanus toxoid and a smallpox vaccination. Her mother stated there had been a "large reaction" to the latter and that the entire upper arm was swollen and inflamed for several days.

The past history disclosed that the patient had received a series of diphtheria-pertussis-tetanus inoculations at 6 months of age and also a smallpox vaccination which was unsuccessful. The only previous illnesses had been measles and mumps at the age of one year. Visual acuity was always excellent and had been tested at school two months before the onset of the present illness. On ocular examination visual acuity in the right eye was found to be 6/100 and J 13, not improvable with lenses. There was no light perception and no direct pupillary reflex in the left eye, although accommodative and consensual reflexes were normal. The eyes were tender to pressure and movement. Funduscopic examination of the right eye showed clear media,

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1. (*a*) Duke-Elder, W. S.: Text-Book of Ophthalmology, St. Louis, 1940, Vol. 3, pp. 2992-2993. (*b*) Walsh, F. B.: Clinical Neuro-Ophthalomolgy, Baltimore, Williams & Wilkins Company, 1947, pp. 562-563.

2. Duke-Elder,[1a] p. 2997.

3. Cormack, H. S., and Anderson, L. A. P.: Bilateral Papillitis Following Antirabic Inoculation: Recovery, Brit. J. Ophth. **18**:167 (March) 1934.

4. Hasabe, cited by Duke-Elder.[1]

5. Ross, J. V. M.: Bilateral Optic Neuritis with Partial Internal Ophthalmoplegia Following Administration of Diphtheria Toxoid, Alum Precipitated, Refined, Eye, Ear, Nose & Throat Month. **28**:119 (March) 1949.

6. Siegert, P.: Sehnervenerkrankungen nach Diphtherieschutzimpfung, Deutsche med. Wchnschr. **74**:769 (June 17) 1949.

a hyperemic disc with blurred margins, and a barely visible physiologic depression. The veins were slightly distended and tortuous, but pulsated with only slight pressure on the globe. No hemorrhages or exudates were present. The macular area, the arterioles, and the periphery appeared entirely normal. The findings on funduscopic examination of the left eye were identical with that of the right eye except that blurring of the disc margins and venous engorgement were more marked. Visual field of the right eye with a 2 mm. white test object at 1 meter disclosed a central scotoma approximately 15 cm. in diameter. There was a generalized constriction of the field to about 30 degrees, and the blind spot could not be outlined.

The patient was admitted to the University Hospital, where the results of a general physical examination were normal except for a large crusting area at the site of vaccination on the left deltoid. Findings on neurologic examination were entirely normal. Results of complete hematological studies were normal, except for an elevated sedimentation rate of 34 mm. in one hour. The blood Kahn test showed negative results. Findings on urinalysis were normal. Chest and skull x-rays including optic foramina showed nothing significant. Lumbar puncture performed three days after admission disclosed a clear colorless spinal fluid with a pressure of 120 mm. of water and 3 to 4 cells per cubic millimeter, a total protein of 19 mg. per 100 cc., normal colloidal gold curve and mastic test, and negative reaction to the Kahn test.

Treatment with 20 U. S. P. units of corticotropin and 15 mg. of mannitol hexanitrate every 8 hours was begun immediately. The patient was hospitalized a total of 12 days and during the entire stay remained afebrile and well. Visual fields, taken at almost daily intervals, showed prompt and progressive improvement. On May 21, four days after admission, the patient had 3/60 vision with the right eye and could count fingers at one foot with the left eye. The visual field of the right eye was 40 degrees with a 2 mm. white test object at one meter, and a 9 cm. by 12 cm. blind spot could be outlined. A full light field was present in the left eye.

At the time of discharge, on May 28, 1952, the right fundus appeared normal except for a slight fullness of the retinal veins. There was a similar finding in the left fundus, and the disc margins remained slightly blurred. Visual acuity was 6/9 with the right eye and finger counting at 2 ft. with the left. Visual fields of the right eye were normal, but in the left eye a central scotoma 14 cm. in diameter was demonstrated with an 8 mm. white test object at one meter.

The patient was followed in the clinic for a period of five weeks. During this period she received long-acting corticotropin in gradually decreasing dosages. On July 23, 1952, visual acuity of both eyes was 6/6 minus 3 letters, and no scotoma could be demonstrated in either eye. Six months later the child had remained well, and no pallor of the discs was evident.

COMMENT

Rosen[7] has stressed that ocular complications such as keratitis and central serous retinitis occurring within a specific period after vaccination are a part of a postvaccinal ocular syndrome. The interval he considered most specific was from 7 to 12 days following vaccination, yet he described complications occurring up to 21 days following vaccination. He felt the appearance of symptoms elsewhere in the body in this interval should be regarded as significant. This impression is substantiated by Winkelman,[8] who, in a review of the literature of postvaccinal peripheral nerve and root disturbances, concluded that these disturbances occur after a relatively constant incubation period of from 7 to 14 days.

7. Rosen, E.: The Significance of Ocular Complications Following Vaccination, Brit. J. Ophth. **33**:358 (June) 1949.

8. Winkelman, N. W., Jr.: Peripheral Nerve and Root Disturbances Following Vaccination Against Smallpox: Study of 5 Cases, Arch. Neurol. & Psychiat. **62**:421 (Oct.) 1949.

The three cases of optic neuritis following diphtheria toxoid reported by Siegert [6] closely resemble the case just described in that 6 to 12 days following immunization there was the acute onset of bilateral optic neuritis in children who remained otherwise well. None of the children suffered permanent visual impairment.

Which was the actual etiological agent, the diphtheria toxoid, the tetanus toxoid, or the smallpox vaccination, in the case just described, cannot be definitely stated, for all have been established as capable of neuropathic action. The allergic theory which is favored by most authorities to explain postvaccinal and serum complications could seem to apply in any case. The characteristic incubation period, the promptness of onset, and the lack of other causal factors indicate that the optic neuritis was indeed a complication of the immunization procedure.

Corticotropin was used in the treatment of this patient because of the success by Quinn and Wolfson [9] in obtaining remission of cases of acute optic neuritis and other posterior ocular segment inflammatory disorders with such therapy. The prompt improvement of the patient's visual acuity within four days after this therapy was begun suggests that this therapy was beneficial.

SUMMARY

A case of acute, bilateral optic neuritis following a booster dose of diphtheria-tetanus toxoid and smallpox vaccination in a 7-year-old child is reported. This case represents a rarely reported ocular complication of such immunization.

9. Quinn, J. R., and Wolfson, W. Q.: Improved Results from Individualized Intensive Hormonal Treatment in Certain Eye Diseases Reported to Respond Poorly to ACTH or Cortisone, Univ. Michigan M. Bull. **18**:1 (Jan.) 1952.

Case Reports

EPENDYMOMA OF THE FOURTH VENTRICLE IN AN INFANT UNDER ONE YEAR OF AGE

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BRAIN tumors occur infrequently during the first years of life and usually are not recognized as such prior to surgical exploration or autopsy examination. In a recent hospital admission an infant was observed who presented signs and symptoms suggestive of a lesion in the cerebellopontine region. These findings, to be described more fully later, led to a presumptive diagnosis of a brain tumor which was later confirmed at autopsy.

REPORT OF CASE

G. W., an 11-month-old Negro girl, was admitted to Kings County Hospital (State University Division) on Oct. 27, 1951, because of a stiff neck of one day's duration.

Approximately two weeks prior to admission the infant became anorectic, showed evidence of weight loss, and reacted with increased irritability on being handled. Three days prior to admission the mother observed that the infant had become less irritable, moderately lethargic, and unresponsive to environmental stimuli.

No history of fever, cough, diarrhea, tremors, or convulsions was noted. There was no history of trauma or drug or lead ingestion.

The baby was born at term to a quadrigravida quadripara mother following a full-term normal spontaneous delivery. She held her head up at 10 weeks, was able to sit unaided at 6 months, and could stand at 9 months.

Physical examination at the time of admission revealed a well-developed but undernourished infant. Though awake and in no acute distress, the infant appeared to be unaware of her surroundings. She had a weak cry and responded poorly to proprioceptive stimuli. The temperature was 37 C. (98.6 F.); the pulse was regular at 90 beats per minute. No rash or petechia was noted. The head circumference measured 44 cm. and the chest circumference 42 cm. The neck was stiff, but the Kernig and Brudzinski reflexes were absent. The anterior fontanelle was bulging slightly and pulsating. A left internal strabismus was noted, which, according to the mother, was present at birth. There was ptosis of the right lid. The infant perceived light, and, except for a left sixth-nerve palsy, ocular movements were normal. The pupils reacted to light, and funduscopic examination revealed no evidence of papilledema. A partial right-sided peripheral facial palsy was noted. The infant had a good gag reflex and sucked well. The tongue deviated obliquely to the right. There appeared to be no motor or sensory loss in the extremities. The deep tendon reflexes were present, and there was a questionable Babinski reflex on the right.

Laboratory Data.—Blood studies showed the following: hemoglobin 12.5 gm. per 100 cc.; white blood cell count 15,000 per cubic millimeter, with 64% neutrophiles, 34% lymphocytes, and 2% monocytes. Findings on urinalysis were negative. The spinal fluid was clear with 300 cells per cubic millimeter, which were predominantly neutrophiles. The spinal fluid protein was 52

From the Pediatric Department of the Kings County Hospital (State University Division).

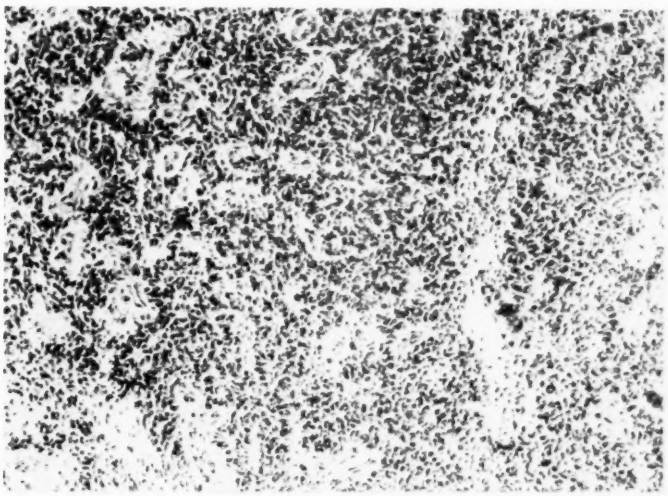

Fig. 1.—Photomicrograph of ependymal tumor showing solid sheets of cells arranged radially about blood vessels or strands of connective tissue; × 100.

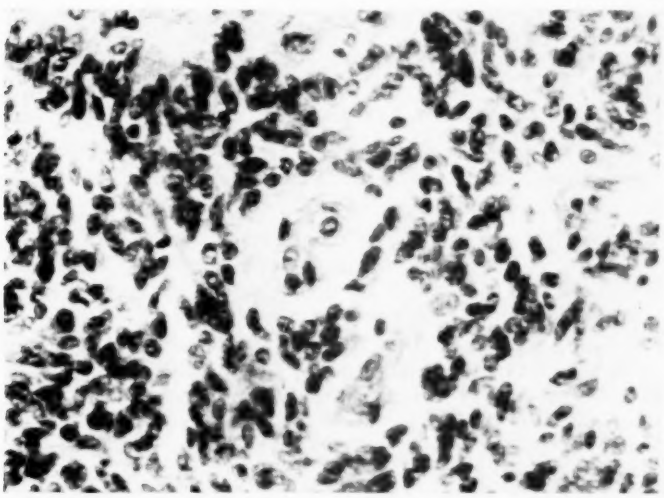

Fig. 2.—Photomicrograph of ependymal tumor showing clear space between the tumor cells and vessel wall; × 400.

mg. per 100 cc., sugar 50 mg. per 100 cc., and chlorides 702 mg. per 100 cc. The smear and the culture for organisms were negative. Blood chemistry studies revealed the following: Mazzini test, negative blood sugar, 98 mg. per 100 cc., and blood urea, 21 mg. per 100 cc. Blood, nose, and throat cultures were negative. An intradermal test with old tuberculin 1:1,000 was negative. Roentgenograms of the skull showed some separation of the cranial sutures with no evidence of calcification.

A presumptive diagnosis of an expanding intracranial tumor was made.

Hospital Course.—During the hospital stay the infant accepted feedings very slowly. Approximately 48 hours after admission she had a generalized convulsion and went into coma: she died 10 hours later.

Pathologic Report.—The postmortem examination was done by Dr. L. M. Friedland. An irregular mass 5 cm. by 5 cm. by 4 cm. occupied the mid-portion of the cerebellum involving the vermis, filling the fourth ventricle, and extending down the middle and inferior cerebellar penduncles to invade and destroy the lower pons and the upper and lower medulla. The left side of the brain showed far more destruction than the right. The basilar artery was partially buried in the neoplasm, the latter extending into the leptomeninges overlying the brain stem.

The tumor consisted of a firm pinkish-gray hemorrhagic structure which in places was sharply demarcated from and in other places merged into the surrounding medullary substance.

There was dilation of the entire ventricular system. An irregular cavity 1 cm. in diameter was present in the medullary substance of the right frontal lobe just lateral to the corpus callosum.

On microscopic examination the tumor was seen to be composed of solid sheets of cells with round vesicular nuclei arranged radially about the blood vessels or strands of connective tissue. Between the blood vessel wall and the tumor cells was a clear space. The tumor cells showed scant barely discernable cytoplasm and indistinct cell outlines. There were regions of necrosis which were infiltrated by multitudes of neutrophiles and fewer eosinophiles. Scattered portions of the tumor show marked cellularity, and in these regions rare mitoses were seen (Figs. 1 and 2).

Microscopic examination of the cavity showed a ragged walled cavity surrounded by a thin zone of poorly staining necrotic-looking white matter. No tumor cells were seen.

Pathologic Diagnosis.—Ependymoma of the fourth ventricle.

COMMENT

Surveys on the incidence of brain tumors in children reported from medical centers in the United States and Great Britain [1] indicate the rarity with which intracranial neoplasms occur during the first year of life. However, Arnstein and co-workers [2] found 13 reports of brain tumor in the neonatal period and added a case of an angioma of the choroid plexus in a 3-day-old infant. Leibner [3] recently reported on the clinical and anatomical findings in seven cases of brain tumors in

1. (*a*) Bailey, P.; Buchanan, D. N., and Bucy, P. C.: Intracranial Tumors of Infancy and Childhood, Chicago, Univ. Chicago Press, 1939. (*b*) Globus, J. H.; Zucker, J. M., and Rubinstein, J. M.: Tumors of the Brain in Children and Adolescents: Clinical and Anatomic Survey of 92 Verified Cases, Am. J. Dis. Child. **65**:604, 1943. (*c*) French, L. A.: Brain Tumors in Children, Minnesota Med. **31**:867, 1948. (*d*) Stern, R. O.: Cerebral Tumours in Children, Arch. Dis. Childhood **12**:291, 1937. (*e*) Critchley, M.: Brain Tumours in Children: Their General Symptomatology, Brit. J. Child. Dis. **22**:251, 1925. (*f*) Cushing, H.: Intracranial Tumors of Preadolescence, Am. J. Dis. Child. **33**:551, 1927. (*g*) Smith, W. A., and Fincher, E. F.: Intracranial Tumors in Children: Preliminary Study of 100 Cases, South. M. J. **35**:547, 1942. (*h*) Craig, W. M.; Keith, H. M., and Kernohan, J. W.: Tumors of the Brain Occurring in Childhood, Acta psychiat. et neurol. scandinav. **24**:375, 1949.

2. Arnstein, L. H.; Boldrey, E., and Naffziger, H. C.: Case Report and Survey of Brain Tumors During Neonatal Period, J. Neurosurg. **8**:315, 1951.

3. Leibner, I. W.: Brain Tumors in Infancy, Pediatrics **1**:346, 1948.

infancy. Gross [4] reviewed the literature on brain tumors occurring during the first two years of life. He cited nine cases which had been reported from 1861-1931 and added nine cases of his own.

Though brain tumors occurring in childhood are predominantly subtentorial, this site of predilection does not seem to occur in infancy.[5] Gliomas comprise 70 to 80% [6] of all brain tumors found in children. Of these, the ependymoma, a rare type of glioma, comprises approximately 3.7% of the total.[6j] In the past 25 years seven cases of ependymal tumors occurring in infancy have been reported in the English literature.[7]

The diagnosis of an intracranial tumor in infancy is difficult. The general symptomatology of increasing anorexia, vomiting, lethargy, irritability, and weight loss with signs of increased intracranial pressure are frequently associated with congenital hydrocephalus or a subdural hematoma. However, when these findings are accompanied by localizing signs and symptoms, for example, convulsions, paresis, ataxia, nystagmus, cranial nerve involvement, and meningeal signs, one must be alerted to the possibility of a brain tumor.

The literature on ependymal tumors has been reviewed by Fisher and co-workers.[6m] Wherever located, they show a pronounced tendency to spread into the ventricles. The subtentorial ependymomas also tend to send long projections of tumor tissue towards or into the spinal canal more than do other gliomas in this region. The stiff neck noted in this patient was probably due to reflex spasms of the muscles of the neck caused by irritation of the dura around the foramen magnum. French [1c] found that 36% of the patients with cerebellar tumors had stiff necks when first seen.

Involvement of one of the last six cranial nerves (other than the eighth cranial nerve) is suggestive of a tumor localized in the brain stem. The facial nerve is the most frequently involved cranial nerve. Though the greatest portion of the tumor was on the left, pressure on the right facial nerve as it entered the internal auditory meatus may have caused the right peripheral facial paresis. Cooper and co-workers [6n] have commented on the resistance of axis cylinders and ganglion cells to pressure phenomenon, accounting for the paucity of neurological findings in the presence of large intracranial tumors.

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4. Gross, S. W.: Tumors of the Brain in Infancy: Clinical and Pathologic Study, Am. J. Dis. Child. **48**:739, 1934.

5. Footnotes *2*, *3* and 4.

6. (*a*) French.[1c] (*b*) Stern.[1d] (*c*) Critchley.[1e] (*d*) Cushing.[1f] (*e*) Smith and Fincher.[1g] (*f*) Craig, Keith, and Kernohan.[1h] (*g*) Arnstein, Boldrey, and Naffziger.[2] (*h*) Leibner.[3] (*i*) Gross.[4] (*j*) Scheinker, I. M.: Neurosurgical Pathology, Springfield, Charles C Thomas, 1948. (*k*) Cleveland, D.: Brain Tumors in Children, Wisconsin M. J. **48**:686, 1949. (*l*) Canavan, M. M., and Hemsath, F. A.: Glioma in the Fourth Ventricle of a Prematurely Born Infant, Arch. Neurol. & Psychiat. **26**:1234, 1931. (*m*) Fisher, E. R.; Hazard, J. B., and Gardner, W. J.: Intracranial Ependymoma: Clinicopathologic Observations, Cleveland Clin. Quart. **18**:260, 1951. (*n*) Cooper, I. S.; Kernohan, J. W., and Craig, W. M.: Tumors of the Medulla Oblongata, A. M. A. Arch. Neurol. & Psychiat. **67**:269, 1952. (*o*) Merritt, H. H.: Cerebrospinal Fluid in Cases of Tumor of the Brain, Arch. Neurol. & Psychiat. **34**:1175, 1935. (*p*) Henderson, W. R., and de Gutiérrez-Mahoney, C. G.: Cerebrospinal Fluid in 302 Cases of Intracranial Tumor, Abscess, and Subdural Haemotoma, Brit. M. J. **4668**:1461, 1950.

7. Footnotes 1*a*, *b*, *d*, and *h* and 6*k* and *l*.

Spinal-fluid examination is usually of little value in diagnosing or localizing brain tumors in infancy. Merritt [6o] and Henderson [6p] have shown that brain tumors in certain locations may produce a pleocytosis and increased protein in the cerebrospinal fluid. This may be due to an aseptic meningeal reaction, necrosis of the brain, or the presence of tumor tissue near the ventricular system. The possibility that the pleocytosis in the spinal fluid found in this patient may have been due to spinal metastasis could not be ruled out, because autopsy of the spinal cord was not performed.

Though ependymomas are usually slow in growing, firm, and enucleable, there is general agreement that these tumors are malignant due to site.[6m] In our patient a terminal convulsion and death occurred soon after admission, preventing any consideration of surgical exploration.

SUMMARY

A case of an ependymoma of the fourth ventricle in an 11-month-old infant is reported.

Society Transactions

AMERICAN PEDIATRIC SOCIETY

Irvine McQuarrie, M.D., *President*
Sixty-Third Annual Meeting
Atlantic City, N. J., May 6, 7, and 8, 1953

(Concluded from Page 481)

The Equilibrium Between Circulating and Extravascular Plasma Proteins. Dr. David Gitlin (by invitation), and Dr. Charles A. Janeway, Boston.

The fact that plasma proteins can leave the circulation quite rapidly when the blood volume is raised above the normal by an injection of blood, plasma, albumin, or a plasma substitute has been recognized for a long time. Moreover, the return of plasma protein to the circulation in sufficient quantities to restore the blood volume to normal in the first days following a severe hemorrhage has likewise been described in the literature.

In a series of investigations on the injection of heterologous native and labeled plasma proteins into man and experimental animals, it has been clearly demonstrated that during the first 24 to 48 hours after injection, the injected protein disappears more rapidly from the circulation than it does in the state of steady logarithmic decline which is established after about two days.

In recent studies of the disappearance of intravenously administered fibrinogen from the blood of patients with congenital afibrinogenemia, approximately half of the infused fibrinogen disappeared from the circulation during the first two days. It was also demonstrated that whereas considerable fibrinogen is found in normal human connective tissues, the connective tissues in sections of the muscle and skin from a patient with congenital afibrinogenemia were almost totally deficient in fibrinogen; this deficit could be quickly rectified by intravenous infusion of fibrinogen. Similar results have been obtained for plasma γ-globulin in a study of its disappearance from the plasma and its appearance in extra vascular sites after injection into patients deficient in this protein.

By an immunohistochemical method, large amounts of plasma albumin γ-globulin, iron-binding globulin, and β-lipoprotein, as well as fibrinogen, have been demonstrated in connective tissues and in cells of many organs in infants and children. It has also been shown that antibodies and even native heterologous proteins present in this extravascular pool can move rapidly into the circulation upon depletion of the specific protein.

These findings appear to be in accord with certain general principles: 1. Under normal conditions of capillary permeability, the volume of distribution of a plasma protein is roughly twice the plasma volume; the mass of exchangeable plasma protein present extravascularly, including that present intracellularly, is approximately equal to the mass of circulating plasma protein within the blood vessels. 2. The extravascular plasma protein is in dynamic equilibrium with the intravascular plasma protein; once equilibrium is established, a decrease in the mass of plasma protein in one compartment results in the movement of plasma protein to that compartment until equilibrium is again attained.

These general principles are important in understanding and treating certain disease processes. For example, in the repair of plasma-protein deficits by replacement therapy, the aim should be repair of both the extravascular and the intravascular deficit, except in those instances where depletion of the circulating protein has occurred too rapidly and recently for equilibration (hemorrhage). These concepts also serve to explain why Rh antibodies or serum bilirubin may increase after replacement transfusion in erythroblastosis fetalis.

DISCUSSION

DR. SAMUEL Z. LEVINE, New York: Bearing in mind what Dr. McQuarrie said, that this discussion was a continuation of this morning's discussion, I wonder whether Dr. Gitlin and Dr. Janeway have determined the complement in the extracellular fluids. If there is this equilibrium between extracellular fluids and tissue and serum, is it possible that the lower serum complement found in nephrotic patients described by Dr. Lange might be the result of dilution of complement in the extracellular spaces, and that with the subsidence of edema, there would be an elevation in serum complement?

DR. HENRY L. BARNETT, New York: I should like to ask Dr. Janeway if he has any data on the earlier part of the disappearance curve. That is, what is the shape of the curve representing the 50% fall in two days?

DR. BENJAMIN M. KAGAN, Chicago: In various disease states, there is a tendency for the globulin value to become elevated. On the other hand, it is rare for the serum albumin value to become elevated. Even in dehydration in human beings, it is unusual to see the serum albumin value elevated above 5.5 gm. per 100 cc.

In dogs subjected to acute dehydration we observed that the serum globulin value tended to keep going up, whereas the serum albumin value became elevated briefly, reached a certain point, and then tended to level off.

I should like to ask Dr. Janeway whether he and Dr. Gitlin have been able to find out where this serum albumin may be going. If it is going into the extravascular areas, is it then readily available again to return to the circulation once hydration has been reestablished?

DR. KURT LANGE, New York: I should like to ask Dr. Janeway what exact part of the capillary he visualizes the albumin to go through. Do you believe it diffuses through the epithelium of the capillary, or do you think it escapes at the cement spaces?

DR. DOROTHY H. ANDERSON, New York: This is of interest to me because of my interest in low-protein states, both of dietary and of other origins. It provides an explanation of the observation that in chronic hypoproteinemia the protein seen in sections of liver, pancreas, and other organs appears extremely low, corresponding, approximately, to the serum protein. This is true, for example, in our fatal cases of celiac disease. Histologically, the tissue proteins in a case correspond approximately with the protein levels of the serum.

DR. CHARLES A. JANEWAY, Boston: Thank you for a lot of interesting questions. Most of them cannot be answered, I am afraid. Dr. Levine's question is extremely relevant. As far as albumin goes, it probably is because of the tremendous reservoir of extracellular fluid in nephrosis, when there is edema, that there is a good deal more albumin, or a larger proportion, out of the circulation than under ordinary circumstances.

As far as Dr. Barnett's remarks go, he is quite right that the disappearance curve isn't two straight lines, but is a smoothly rounded slope which gradually comes down and becomes a straight line. We have a lot of data on levels every 15 minutes to every half hour during the early part of the fall.

As to Dr. Kagan's question, I cannot answer it. I think it is very probable, however, that because of the small molecular size of albumin it can move out of normal capillaries more rapidly than some of the globulins.

As for Dr. Lange's question about whether it goes through endothelial cells or the cement substance, we cannot say anything about that. Dr. Anderson's observations are very very interesting. The relation between tissue proteins and circulating proteins is something that has to be studied. For example, it is very hard to detect much serum albumin as immunologically reactive with a specific strain in the parenchymal cells of the liver, except in the nuclei, with much less in the cytoplasm, where certainly I should expect it.

As to Dr. McQuarrie's remarks, I can only refer back to one study, made in 1943, by Dr. Heyl and Dr. Oliver Cope, in which we had cannulae in about every lymphatic in the body in a dog. When bovine albumin was administered intravenously, it gradually tended to come into equilibrium all over the body. The bovine albumin increased in the lymph as it fell in the plasma. The thoracic duct lymph has a higher protein concentration than lymph from extremities.

The Role of Potassium in the Prevention of Alkalosis. Dr. Robert E. Cooke, Dr. William E. Segar, Dr. Daniel C. Darrow, Claude Reed, A.B., Donnell Etzwiler, A.B., Saul Brusilow, A.B., and Martin Vita, A.B., New Haven, Conn.

The development of alkalosis depends on the failure to preserve body chloride or to excrete bicarbonate when loads of alkali are presented for renal excretion. A series of experiments was designed to study the role of potassium in this regulation.

Loads of sodium bicarbonate were administered to normal rats in drinking water along with known amounts of potassium. These animals were able to excrete 20 to 30 mEq. per kilogram of body weight of bicarbonate per day without potassium deficiency or hypochloremic alkalosis developing as long as the intake of potassium chloride exceeded 0.4 mEq. per kilogram of body weight per day. Obviously, therefore, the amount of bicarbonate excreted with potassium was insignificant. However, a small intake of potassium is necessary to permit maximal renal tubular reabsorption of chloride or excretion of bicarbonate.

In acute loading experiments, 15 mM. per kilogram of body weight of sodium bicarbonate was injected intraperitoneally into normal rats and rats made potassium deficient by two weeks of low-potassium diet and desoxycorticosterone (Doca). Urine was collected for the succeeding 12 hours. Serum and muscle were analyzed at the end of that time also.

The normal animals after 12 hours had no change in extracellular composition except for a slight fall in serum potassium concentration. The large uptake of sodium by muscle in normal rats accounted in part for the absence of alkalosis.

In the potassium-deficient group, hypochloremic alkalosis was severe after loading. The muscle sodium value did not rise; the muscle potassium value did not fall further after loading.

Excretion of the water load was limited in the potassium-deficient animals. The excretion of chloride was fivefold greater in the deficient animals than in the normal animals, even though serum chloride was low in this group.

When potassium bicarbonate, 3 mM. per kilogram of body weight twice a day, was administered for five days, complete correction of the alkalosis resulted. Both serum bicarbonate and chloride concentrations returned to normal. The correction was effected by the excretion of sodium and extracellular water without chloride.

Urine bicarbonate excretion rose only slightly despite the administration of potassium bicarbonate. Urine pH and titratable acidity remained relatively constant throughout the experiment.

The excretion of sodium and potassium was accompanied by the excretion of large quantities of organic anion. Part of this organic anion was demonstrated to be citrate. The excretion of citrate increased fifty- to one-hundred-fold.

The excretion of organic anion in place of chloride permits the excretion of sodium without chloride and without change in urinary pH in the renal defense against alkalosis. Such a mechanism is analogous to the substitution of ammonia for sodium in the renal defense against acidosis. Potassium would seem to be of importance in this mechanism.

DISCUSSION

Dr. James L. Gamble, Boston: I wish to express my admiration for this finding which uncovers a new factor in the control of acid-base excretion in the urine.

We are familiar with the regulated use of the organic base ammonium in defense of the fixed base of the body fluids. So it is interesting and appropriate to find an organic acid that can be adjustably placed in the urine in order to conserve fixed acid, especially the structurally very important anion, chloride. We have been accustomed to regard the regulated removal of carbonic acid in the urine as adequately serving this end, but we should not be surprised to find that other organic acid substances, produced in the course of carbohydrate metabolism, may be used in this way.

Dr. George M. Guest, Cincinnati: It is well known that changes in excretion of phosphates play an important role in regulating acid-base equilibrium of the blood in conditions of metabolic acidosis. Have you studied urinary phosphate excretion in these states of alkalosis with potassium deficiency?

Dr. L. Holliday, Indianapolis: I should like to draw a distinction between the alkalosis observed here and that observed with chloride depletion. These animals, it is true, conserve

chloride, but, actually, their total body chloride is at least normal, if not in excess of normal, as has been previously demonstrated. It is curious that the kidney conserves chloride with this mechanism, and the animal thereby becomes edematous.

What this means in terms of renal physiology is one of the questions that I think has been raised.

DR. IRVINE MCQUARRIE, Minneapolis: I have been very much interested in following the work in Darrow's laboratory. Sixteen years ago, when we first encountered very similar changes in the acid-base metabolism in a severe case of Cushing's syndrome, I remember our trying the effects of various other bases, as well as potassium and acids. The only treatment that proved to be specific for this type of alkalosis in Cushing's syndrome was potassium administration, as reported by Dr. Cooke. It would be interesting to know whether in this state one would find an increased excretion of citrate, as reported in Cushing's syndrome. I wonder if this group has had experience with this.

DR. ROBERT E. COOKE, New Haven, Conn.: I should like to thank Dr. Gamble very much. It is a tremendous tribute to receive his praise. In regard to Dr. Guest, I should like to point out that these experiments are rather unusually contrived, in that the usual materials that are supplied in diet have been markedly restricted during these experiments. That is, phosphorus intake was very low, and I am sure that if there had been a high phosphorus intake, this would have played a greater role in the excretion of cation.

As regards the difference between chloride depletion and the type of alkalosis that we have studied, we actually feel that in chloride depletion there is also a loss of body potassium, as Dr. Holliday and a number of people have pointed out. We do think, however, that if renal function can be maintained during such experiments, that in the presence of adequate potassium there might possibly be a correction of this type of alkalosis by shrinking down extracellular fluid around the remaining chloride.

I think I should point out, although no one asked this, that such therapy would not be safe to apply to human patients at this time, that is, the correction of alkalosis with potassium bicarbonate. I was hoping that Dr. Pratt would have an opportunity to recount the story of a patient whose alkalosis was actually corrected in this way by mistake a number of years ago. In this case there was a severe hypochloremic alkalosis associated with edema. Large amounts of potassium bicarbonate were given instead of potassium chloride. The alkalosis was corrected, but in so doing his extracellular volume was so depleted that he went into shock.

The Renal Response of Premature Infants to Administration of Bicarbonate and Potassium. DR. FOLKE TUDVAD (by invitation), HELEN MCNAMARA, M.A. (by invitation), and DR. HENRY L. BARNETT, New York.

The observations to be described were undertaken in an attempt to answer the following questions: 1. Does renal immaturity play a role in the "physiologic" acidosis of the premature infant? 2. Can this acidosis be corrected by the administration of bicarbonate? 3. Is the premature infant able to excrete potassium as readily as the adult? The answers to these questions possess both physiologic and clinical interest.

Measurements were made in premature infants of glomerular filtration rate, concentrations of serum, and urinary electrolytes and urinary pH during infusions of bicarbonate and of potassium and following injections of a carbonic anhydrase inhibitor, 6063.

The results indicated that the acidosis of "healthy" premature infants is not due to immaturity of kidney function involving a lower maximum rate of tubular reabsorption of bicarbonate; consequently, if other factors were not involved, serum bicarbonate concentrations in the premature infant would be stabilized in the same range as those of the adult. It follows from the above that the "physiologic" acidosis of the premature infant can be corrected by the administration of bicarbonate. Finally, it was observed that potassium can be excreted very readily by the premature infant. For example, following an injection of 6063 given during the infusion of both potassium and bicarbonate, the rate of excretion of potassium reached 170% of the quantity filtered per minute, indicating tubular secretion of potassium.

There are certain direct clinical applications of these results. Although it is generally agreed at present that correction of the "physiologic" acidosis of the premature infant is not indicated, further knowledge may reveal circumstances where it is desirable to increase serum bicarbonate.

If so, the present results show that such correction of the acidosis is possible. The observations on potassium excretion have very clear clinical application. Safe treatment of intracellular potassium deficiency by the administration of potassium is dependent in large part upon the ability of the kidney to excrete potassium rapidly in the presence of high serum-potassium concentrations. The demonstration that potassium can be excreted rapidly by the premature infant suggests that immaturity of kidney function in the permature infant imposes no additional limitation on the rate at which potassium can be given.

DISCUSSION

DR. WALLACE W. MCCRORY, Philadelphia: I wish to congratulate the authors for the elegant studies they have conducted on an aspect of renal function in premature infants that is of fundamental physiologic interest. I should like to know whether they have data on the actual rates (corrected to 1.73 sq. meters surface area) of the titratable acid and ammonia excretion observed in the infants before the experimental observations were performed. The only other point is in regard to the value of the adult as a parameter for evaluation of renal function in the premature infant. I should like to know whether the authors feel that there is justification for comparisons involving premature infants and adults. One can obviously define limitations by this approach. I wonder if it might be more rewarding, however, to change our perspective and evaluate some of the biochemical aberrations as reflections of the limitations the pediatrician faces in replacing the maternal placenta. In this way we might emphasize more clearly the ability of the premature infant with proper awareness of the difficulties we face in providing a nutritional load that would be defined as optional when it does not exceed what would appear to be (by comparison to normal infants) respectable abilities on the part of the premature infant for renal excretion of electrolyte, titratable acid, and ammonia and for bicarbonate reabsorption.

DR. SOLOMON KAPLAN, Cincinnati: The study of the mechanism of bicarbonate excretion is very topical. Recently, it has been shown, by two independent laboratories in New York, that the excretion of bicarbonate is directly related to the pCO_2 of the plasma. I believe that these observations were made completely independently.

The question I would like to ask Dr. Barnett is this. Will he speculate on what the relationship is between the pCO_2 and the rate of bicarbonate excretion in premature infants? If a plot is made of bicarbonate reabsorption versus pCO_2, the points form a straight line with a positive slope in adults. When the pCO_2 is low, irrespective of total bicarbonate content, the rate of reabsorption of bicarbonate by the kidney is low. This interesting finding, of course, might have been predicted from the Henderson-Hasselbalch equation.

The second observation made by Dr. Barnett is extremely important, namely, the extraordinary ability that premature infants appear to have to excrete potassium. Some of the infants showed rates of excretion of potassium which were quite large. This is indeed a very useful fact to know when one is administering potassium to premature infants.

DR. ROBERT E. COOKE, New Haven, Conn.: I don't in any way want to disparage the very beautiful and clear-cut studies of Dr. Barnett. The work involved must have been tremendous. I think it is worth pointing out that the capacity to do something is entirely different from what the kidney may actually do under most circumstances.

The concentration of bicarbonate in the reabsorbate will be the concentration that is found in the extracellular fluid. It could be anything else, or else normal serum plasma concentration would not be 26 mEq. per liter. If the reabsorbate had a concentration any different from that of the plasma, we would have marked alterations in body composition.

In a respiratory acidosis, the reabsorption of bicarbonate is markedly increased, and we establish a serum bicarbonate level, let us say, of 35 mEq. per liter. Likewise, in respiratory alkalosis, where there is undoubtedly a change in intracellular pH, we similarly have a low reabsorption of bicarbonate per liter of glomerular filtrate.

In potassium deficiency, without question, 30 or 35 mEq. of bicarbonate per liter of glomerular filtrate is reabsorbed. If it had been any different, the plasma concentration would have been markedly altered.

DR. DANIEL C. DARROW, New Haven, Conn.: I would like to add the following to Dr. Cooke's remarks. Because of the large quantities of glomerular filtrate, preservation of body composition is ultimately dependent on reabsorption of appropriate amounts of water and elec-

trolyte from the glomerular filtrate. The ratio of the Na to Cl reabsorbed indicates the chief renal function determining the acid-base equilibrium of plasma. The amounts of Cl in relation to Na which are reabsorbed seem to be dependent on cell pH rather than extracellular pH. However, owing to the reciprocal relationship of Cl to bicarbonate, the data may be expressed in terms of the ratio of bicarbonate to Na reabsorption from glomerular filtrate.

DR. HENRY L. BARNETT, New York: In regard to Dr. McCrory's question, from our data we cannot compare the rates of excretion of ammonium and titratable acid in infants and in adults. To really make such a comparison, one would have to do the type of observations done by Gordon, producing acidosis rather than alkalosis.

Dr. McCrory is probably right about the futility of attempting to compare rates of electrolyte excretion in infants and in adults, and we have not done so here. This question also refers to Dr. Cooke's statement that what the infant can do is not necessarily what it does. I think this is right. We have taken issue with Dr. McCance for saying that what the infant does do is what it can do, and I think we would be in as great error if we were saying what Dr. Cooke implies.

The effect of pCO_2 on these tubular functions, as Dr. Kaplan has said, has been investigated. Our data are not sufficient to help answer the question of whether changes in hydrogen ion concentrations or in pCO_2 influences bicarbonate reabsorption. The observations of both Dr. Pitts and Dr. Gilman indicate that it is the latter.

In regard to Dr. Cooke's and Dr. Darrow's statements, I think they indicate a difference in orientation toward the study of kidney function. For instance, Dr. Cooke said that their observations represented studies of kidney function without collecting urines, with which I would agree. However, it is also possible to study renal function by collecting and analyzing urine as we do. It is perfectly obvious, as Dr. Cooke stated, that one would not have to have done any observations to know that an infant in a steady state, who has a concentration of bicarbonate in serum of 20 mEq. per liter must be reabsorbing bicarbonate from the glomerular filtrate at this same concentration.

To repeat, therefore, the question we were asking was, if we raised serum bicarbonate, would the infant reabsorb more as the adult does or does 2 mEq. per 100 ml. of glomerular filtrate represent the maximum rate of tubular reabsorption of bicarbonate in the premature infant? However one chooses to to express it, the answer is no.

The Effect of Added Carbohydrate in the Diet on Water, Nitrogen, and Electrolyte Balances in Premature Infants. DR. PHILIP L. CALCAGNO (by invitation) and DR. MITCHELL I. RUBIN, Buffalo.

The present study was undertaken to determine whether the addition of carbohydrate to milk feeding in premature infants has any influence on renal osmolar and water excretion, since it is known that in the mature person carbohydrate is protein-sparing and that urea, the end product of protein metabolism, makes up from 40 to 60% of the the osmolar load excreted in the urine.

Group 1 was composed of six infants. Three of these were fed a diet containing protein at 20% of the total calories (Formula A) and the other three a diet containing 25% of the total calories (Formula C) as protein. Following this, a second diet was fed to each where 5 gm. of carbohydrate as Dextri-Maltose was added per 100 cc. to the formula (Formulas B and D), thus offering additional Calories as carbohydrates. When given Formulas A and C, the infants received an average of 107 Cal. per kilogram of body weight per day, 5.5 to 6.5 gm. of protein per kilogram per day, and 150 cc. of fluid per kilogram per day. On Formulas B and D, the average total daily caloric intake was 130 Cal. per kilogram of body weight per day. The total protein intake on diets B and D was the same as on A and C. These diets were designed to determine the effect of the added carbohydrate on nitrogen retention at these two levels of protein feeding. Before an average of six-day balance studies was made on these infants, there was a seven-day foreperiod to allow metabolic adjustment to the changed diets.

Group 2 consisted of four premature infants weighing between 1,225 and 1,780 gm. The plan of the study in this group was similar to that of Group 1, with the exception that the two diets fed each infant were isocaloric (around 125 Cal. per kilogram of body weight) and contained the same amount of fluid (150 cc. per kilogram of body weight). The protein Calorie content of this "added-carbohydrate" formula was thus reduced from 21% in the "whole" milk (Formula R) to 16% in this changed formula (Formula G). The concentrated cow's milk offered 7.5 gm. protein

per kilogram of body weight per day, and the carbohydrate modified formula offered 6.1 gm. per kilogram of body weight per day. This formula was designed to determine the effect of added carbohydrate when the infants were fed 150 Calories each. During the added-carbohydrate feeding there was a reduction in the percent composition of protein and fat in the diet. The fluid intake on the two diets was kept constant at 150 cc. per kilogram of body weight per day. Four-day balance collections were made after a foreperiod of seven days on each formula. All diets were relatively high in protein content, since the primary aim of the study was to determine the effect of high osmotic loads on the renal water losses of the premature infant. It must be emphasized that the data reflect a study of only a short period of time in the lives of these infants. How long these balance studies should have continued for the establishment of equilibrium is not known.

In conclusion, the following summarizing remarks may be made.

With added carbohydrate in the formula during these short balance periods there resulted a better weight gain, both while there was a constant nitrogen intake and with a 19% reduction in dietary nitrogen intake.

Nitrogen retention in these premature infants was greater when the nitrogen intake was increased or when the total amount of Calories, as carbohydrate, was increased. Similar changes occurred in sodium and in potassium retentions (sodium and potassium values were not corrected for sweat). Whether these increases in nitrogen retention would persist for longer periods is open to question. There must be a ceiling to the amount of nitrogen that can be retained when growth requirements are satisfied.

Infants fed added carbohydrate had a lower blood-urea-nitrogen value and a decreased urea, sodium, and potassium excretion. Thus the kidney was presented with a lower osmolar load for excretion.

The urine concentration on the various diets is a simple reflection of the load demanding excretion and the available expendable water. In the presence of restricted expendable water, and particularly in the presence of a limited concentrating renal capacity as seen in the premature infant, a diet offering a smaller load for renal excretion would seem desirable.

DISCUSSION

Dr. Robert E. Cooke, New Haven, Conn.: I think Dr. Rubin's point is an extremely important one in infant nutrition. What we are trying to do in the feeding of children essentially is to provide them with the largest margin of safety to meet stress, such as extrarenal losses of water as in diarrhea and as in heat stress.

If one considers any feeding mixture not in terms of so many grams or milliequivalents per liter of material but rather in terms of so much per 100 Cal., because this is essentially the unit of nutrition, one would realize that the addition of carbohydrate reduces the solute load, sodium load, and so forth, per 100 Cal. This finding Dr. Powers pointed out a number of years ago, and it has been confirmed many times since.

We have performed balance studies on patients during heat stress, and, although they are not completed, there would certainly seem to be no controversy with Dr. Rubin.

Dr. Samuel Z. Levine, New York: I don't think anybody would deny the validity of the conclusions of Dr. Rubin. I think one might wonder about the reliability of gross nitrogen-balance studies instead of amino acid nitrogen-balance studies. It seems to me that before one could come to any real conclusion about the type of tissue being stored, one should know what the amino acid-nitrogen output was, especially since the urea nitrogen varied in the two groups.

One might expect with a higher protein intake that more water would be claimed for excretion through the skin and lungs because of the higher metabolism in the protein-fed babies, and that might leave—since the loss through skin and lungs has a prior claim to water excretion—less water for excretion by way of the kidneys.

With high-protein diets, and both groups were on high protein diets, I wonder whether any examination of the urine was made for other solutes, like the intermediary products of phenylalanine and tryosine metabolism, and whether vitamin C was given to these babies.

Dr. James L. Gamble, Boston: Dr. Clement Smith has shown me results of a recent study in which premature infants were given glucose alone along with an ample water intake without

observable sparing of body protein. I was interested by this finding, because in studies on the life-raft ration it was found that in adult subjects an intake of glucose reduced the consumption of body protein to about half the extent measured during fasting. This effect was gained by giving 100 gm. of glucose and could not be increased by a larger intake of glucose nor by providing protein to the extent of the observed loss of protein. In order to obtain nitrogen balance, the caloric value of the food had to be raised to about three-quarters of energy expenditure.

In the experiments which Dr. Calcagno and Dr. Rubin have described, these conditions for maximal sparing of protein by glucose were provided. Discussion of protein-sparing by glucose under quite different circumstances is therefore not directly relevant. The absence in premature infants of the partial sparing of protein by glucose on a low-calory intake observed in adults is, however, an interesting finding which needs to be explained. For this reason I have ventured to present it as a footnote to the excellent paper we have just heard read.

DR. GILBERT B. FORBES, Dallas, Texas: I am very thankful to Dr. Rubin for emphasizing this problem to us again, in view of the rather unfortunate tendency in some parts of the country to feed normal infants diets which contain excessive amounts of protein in relation to water intake.

We had this matter forced upon us recently by the observation of two infants with so-called unexplained fever, in which it became evident shortly that the temperature could be reduced to normal by decreasing the excessive protein intake which had been inadvertently prescribed. One child had been consuming a diet which provided about 25 gm. of protein per kilogram of body weight per day.

I wonder if Dr. Rubin would comment on one other aspect of this matter of the relationship between protein and carbohydrate, and that is the specific dynamic action of protein, whether or not this might be a deleterious factor in feeding infants diets containing large amounts of this substance.

We noted, for example, in these two infants that they did not gain as well during the period of high protein intake as they did during the subsequent period of normal protein intake.

DR. MITCHELL I. RUBIN, Buffalo: Dr. Levine, you asked a question that I cannot answer. We did not do any amino acid determinations—excretions or blood levels. These children were all normal premature babies and were fed vitamin C.

The babies on the high-carbohydrate diets actually excreted fewer milliosmoles per liter than when given the noncarbohydrate diet but also excreted more water. There was a larger retention of water on the noncarbohydrate diet.

I think the disadvantage of the high-protein diet may be related to the very large osmolar load demanding excretion in the urine. This requires a certain amount of water. Whether in your case, Dr. Forbes, the fever was related to a high specific dynamic action of protein only, or whether it was related to dehydration, I don't know.

I appreciate Dr. Gamble's remarks. The information that he brings us, I am sure, is so much more important than what I had to say.

Alkavervir (Veriloid) Treatment of Hypertension in Acute Glomerulonephritis: A Clinical Report. DR. MARSHALL B. KREIDBERG (by invitation) and DR. JAMES MARVIN BATY, Boston.

Hypertension frequently occurs in children during the course of acute glomerulonephritis. Since it is not always responsive to classic magnesium sulfate therapy, whether oral, intramuscular, or intravenous, other safe depressive agents have been sought. The use of alkavervir (Veriloid), an extract of veratrum viride, has been widely reported in the treatment of arterial hypertension.

In our experience, orally administered alkavervir has lowered the blood pressure in six children who had acute glomerulonephritis with hypertension. The children treated were from 5 to 11 years old, their blood pressures ranging from 144/100 to 180/110. When magnesium sulfate in conventional dosage, administered orally and intramuscularly in all, as well as intravenously in one, failed to lower the blood pressure, 1 mg. of alkavervir was given orally three times a day. In five patients the blood pressure was reduced to and maintained at normal levels within 14 to 72

hours after administration of the initial dose. In a child who had anaphylactoid purpura and nephritis, however, the blood pressure was not maintained at normal levels until six days after institution of therapy with alkavervir. The drug was well tolerated and produced no side effects.

In all cases, the previously high nonprotein-nitrogen levels returned to normal after therapy. There was also a decrease in body weight, as well as an increase in urine output. No adverse effects on renal function were noted.

DISCUSSION

DR. MILTON RAPOPORT, Philadelphia: It is interesting to hear that there is another hypotensive agent available. However, there are certain considerations one must keep in mind before this replaces the therapy which most of us are using, or at least which we are using most extensively, magnesium sulfate therapy.

Last year, Dr. McCrory reported some experience we had had with the use of hydralazine (Apresoline), another hypotensive agent, which was quite effective in reducing blood pressure. However, in some of the patients, there were reductions in renal function. While these were in the patients involved to insufficient magnitude to get them into trouble, I think it is known that veratrum viride is also capable of reducing renal function, and, if it is used extensively, I feel quite certain that the patient will be encountered in whom a further reduction in renal function will take place while you are attempting to reduce his blood pressure, which would cause trouble.

DR. ROYCE, Los Angeles: The many drugs that are currently used to control the hypertensive phase of acute nephritis emphasize our present need for a consistently effective hypotensive agent. For the past two years at the Los Angeles Children's Hospital we have been collecting information on the use of intravenously administered alkavervir in acute nephritis. Six children were studied. All of them had severe hypertension and signs suggesting secondary hypertensive phenomena, such as encephalopathy, headache, and nausea. A prompt hypotensive effect was consistently noted following the intravenous administration of alkavervir.

Possibly the two routes of administration may be used in complementary fashion. The hypertensive child who is nauseated or vomiting will initially require the parenteral route. When his gastrointestinal tract is able to tolerate the drug, his blood pressure may then be maintained at the desired level by oral alkavervir therapy.

DR. JAMES N. ETTELDORF, Memphis, Tenn.: We know that veratrum viride has a direct action on the heart, and it does increase the refractory period. I think it would be rather important that electrocardiography be followed on these patients, and I wonder if they had the opportunity to do that on these patients.

DR. WALLACE MCCRORY, Philadelphia: There are two points that I would like information on if these authors can provide it. As background for the studies we reported last year, we examined the clinical histories of a number of patients observed prior to our interest in this subject. We found great variations in terms of time in regard to the onset of the disappearance of hypertension in acute nephritis during the time of hospitalization.

I notice in a number of the charts here that the periods of time in which hypertension abated certainly were of a degree one might expect with spontaneous disappearance of hypertension. I do not feel the effect of alkavervir has been clearly defined. We also found that there is an association of the onset of loss of edema with the disappearance of hypertension in many instances.

I would, in this light, suggest to the authors that the increase in urine flow they observed following withdrawal of alkavervir therapy might indicate that there may have been some suppression of renal function and diuresis usually seen to occur with the loss of hypertension, since diuresis in these patients occurred after abatement of hypertension.

DR. KURT LANGE, New York: I would like to ask Dr. Kreidberg if he has any figures comparing the course of hypertension in the treated group to that in an untreated control group. As Dr. McCrory has stated, most of these patients lose their hypertension very rapidly. In a large group of patients with acute glomerulonephritis which we examined during the last two years, hypertension has never bothered us for any length of time, and I would think that the curves shown here are very similar to ours in which hypertension disappeared rather rapidly, spontaneously.

DR. MARSHALL B. KREIDBERG, Boston: I wish to thank the discussants. When we first started to use alkavervir we did not intend to replace the conventional magnesium sulfate therapy. At the present time, we are undertaking renal-function studies to see exactly what happens to kidney function while these children are being treated with alkavervir.

I wish to thank Dr. Royce for his comments. There was only one child—we followed all these children with electrocardiograms—and there was one child who had electrocardiographic changes of prolonged P-R intervals. He had failure, and it may well be that the improvement that was seen in subsequent electrocardiograms was due to the digitalis therapy.

The question of the time interval on treatment, and whether the child was getting well—we also thought of that, because they had gone along for a number of days with magnesium sulfate therapy. However, in a subsequent group treated with alkavervir right from the start we observed exactly the same effects.

Abnormal Electrolyte Composition of Sweat in Cystic Fibrosis of the Pancreas.

DR. PAUL A. DI SANT'AGNESE (by invitation), DR. ROBERT C. DARLING (by invitation), DR. GEORGE A. PERARA (by invitation), and ETHEL SHEA, B.A. (by invitation), New York

Two groups of cases were investigated, 35 in patients known to have cystic fibrosis of the pancreas and 40 in controls. The second group included patients on the hospital wards, excluding two types of patients—patients with known adrenal insufficiency and members of families of people known to have fibrocystic disease.

Sweat was collected in all instances under a vapor-sealed patch from the midabdominal area, and the patients were subjected to a constant and very mild thermal stimulus in a room at constant temperature (90 F.) and humidity (50%).

The sweat of patients with cystic fibrosis of the pancreas contained an average concentration of chloride and sodium three times and twice, respectively, that found in controls. The potassium levels in the sweat of patients with fibrocystic disease were also increased, although not to the same degree. All of these differences were of great statistical significance. The range of values was quite broad for both groups, but there was virtually no overlap. In contrast to these marked differences in electrolyte composition, the amounts of sweat were not significantly different in patients with fibrocystic disease from those in controls.

From selected controls it is shown that pancreatic deficiency and chronic pulmonary disease per se do not elevate the electrolyte composition of sweat. Patients with acquired pancreatic deficiency have normal sweat chloride and sodium, whereas in patients with fibrocystic disease with partial pancreatic function these sweat electrolyte values are elevated. Detailed metabolic studies in two patients with fibrocystic disease show normal behavior of the kidney in response to salt loss and salt restriction and an adequate response of the adrenal following cotricotropin (ACTH) administration. Thus these two organs appear to be unlikely causes of the high sweat electrolytes in this condition. The fact that the sweat glands do not retain salt effectively in hot weather, during salt restriction, and when desoxycorticosterone (Doca) is administered, points to a disturbance in the sweat glands themselves.

Massive salt depletion through the sweat in warm weather would appear to account satisfactorily for the "heat" casualties in this desease. Further measurements in recent heat casualties clarify the probable mechanisms involved.

In separate studies, the electrolyte composition of duodenal contents and of parotid secretion was also investigated and not found to differ significantly between patients with fibrocystic disease and controls. On the other hand, chloride and sodium in mixed saliva and the parotid secretory rate were found to be higher in patients with cystic fibrosis of the pancreas than in other persons. The latter differences were of statistical significance.

The fact that the sweat glands and the parotid are affected, as well as the pancreas, lungs, and other organs, suggests that the secretory activity of many and perhaps all exocrine glands, mucus-producing and others, is disturbed in cystic fibrosis of the pancreas.

A survey of 50 relatives of patients with this condition indicates that several members of such families have sweat electrolytes which are distinctly high, although somewhat below the range of patients with the manifest disease. These facts raise important questions concerning the presence of mild subclinical forms of the disease. Likewise, examination of the sweat has been found

a useful test in helping to evaluate cases with only part of the syndrome but with some residual pancreatic function. Its use is demonstrated in differentiating between fibrocystic disease of the pancreas, familial dysautonomia, celiac disease, and other chronic lung conditions.

DISCUSSION

DR. GEORGE M. GUEST, Cincinnati: With interest in the state of hypochloremia found under the conditions described, I should like to ask if you have made similar observations on patients with respiratory acidosis from other causes. Can one conclude that it is simply the CO_2 excess in respiratory acidosis that causes an excessive excretion of chloride in the sweat?

DR. IRVINE MCQUARRIE, Minneapolis: I hope Dr. di Sant'Agnese will give us some idea how the sweat was collected.

DR. LYTT GARDNER, Syracuse, N. Y.: I should like to ask if the changes found in the composition of sweat with respect to sodium and chloride show any differences from those observed by Conn and his co-workers and Locke and his co-workers in cases of hypoadrenocorticism.

DR. PAUL A. DI SANT'AGNESE, New York: In answer to the question of Dr. Guest, I have no personal observations on adults with other types of chronic pulmonary disease, and I have to rely on what I am told by others on the subject.

As to the method of collection of the sweat, as I described briefly in the paper, we have collected the sweat from the abdominal area from both sides of the abdomen, with a square dry gauze patch, 12 cm. in area, which is appropriate cover to prevent evaporation and sealed by waterproof adhesive. That is then reweighed in a bottle which has been previously weighed when it was dry. A proper amount of lithium sulfate solution is added and then analyzed for the chloride-sodium-potassium.

As far as the conditions were concerned, they were standardized in the sense that all patients were in a room at a constant temperature, 90 F., and 50% humidity and covered with a similar type of sheet and blanket, so that the conditions were pretty well standardized in all cases.

Observations of body temperature were done on about 15 patients, and there was no rise in body temperature, as the temperature was not very high in the room itself.

As far as the question as to whether electrolytes in the sweat are increased in a different manner from hypoadrenal patients, if I understand the question correctly, they are not, to my knowledge, and that is why we have excluded patients with known adrenal insufficiency among the controls.

The Relationship Between Progressive Muscular Atrophy of Spinal Origin and Amyotonia Congenita. DR. JAMES B. AREY and DR. HENRY W. BAIRD III, Philadelphia.

Various clinical features have been suggested as differentiating amyotonia congenita (Oppenheim) from Werdnig-Hoffman's progressive muscular atrophy of spinal origin. These are summarized in the following tabulation, which is modified from the superb monograph by Brandt dealing with this subject.

Amyotonia Congenita	Progressive Muscular Atrophy of Spinal Origin
Onset at birth	Onset in early infancy
Usually not familial	Often familial
Absence of muscular atrophy	Atrophy of paretic muscles
Generalized hypotonia	Paresis, beginning in pelvic muscles
Absent tendon reflexes	Absence of tendon reflexes corresponding to extent and degree of atrophy
No electrical reaction of degeneration	Reaction of degeneration
Improvement or lack of progression	Progression

Although classic examples of each syndrome do occur, there are so many transitional forms that any such clinical differentiation is obviously arbitrary and of no real value. Even with respect to the last point, i.e., the clinical course of the disease, there is little or no evidence to indicate that significant sustained improvement is common. Furthermore, the rapidity of progression of muscular atrophy of spinal origin may vary, and muscular readjustments during rela-

tively stationary periods may result in apparent improvement. Thus, even transient periods of slight improvement should not be considered as a differential feature, and the prognosis must be considered as uniformly grave, and uncertain only as to the duration of the process.

There remains a small group of infants with generalized hypotonia in whom definite improvement takes place. Since pathologic studies of these infants are not available, accurate classification of this group is obviously impossible; they may well represent a variety of conditions rather than any single disease process.

The pathologic alterations described in patients dying with so-called amyotonia congenita are, for practical purposes, indistinguishable from those observed in infants with progressive muscular atrophy of spinal origin. Pathologic classification of the process into one or the other group apparently depends largely upon the preference of the pathologist for one term or the other and not upon any fundamental difference in the alterations observed.

Detailed histologic studies of the spinal cord, peripheral nerves, and skeletal muscles are reported in three infants dying with progressive muscular atrophy of spinal origin. Histologically, the basic lesion in all three infants was located in the motor nerve cells of the anterior horns of the spinal cord; these cells were diminished both in number and in size. Occasional giant spherical or "balloon" cells with central chromatolysis were demonstrable in all three infants. The changes in the motor nerve cells of the anterior horns were reflected in the ventral nerve rootlets by diminution in the amount of myelin- and of silver-staining fibers within many of these rootlets. Changes in the larger peripheral nerves were inconstant and difficult to interpret. In the small intramuscular nerves, however, definite changes were visualized after staining with silver. There was a striking diminution in the number of silver-staining fibers in the small nerves of affected muscles, when compared to those present in control sections.

Changes in the affected muscles were considered as secondary to the neurologic lesions. They consisted of severe atrophy of many fibers, so that minute, cord-like, and often wavy muscle fibers with well-preserved striations predominated. The atrophic muscle fibers were often grouped in a somewhat lobular fashion. The changes described pathologically in these infants are indistinguishable from those variously described in the literature as occurring in association with amyotonia congenita or with progressive muscular atrophy of spinal origin.

Certain features of the clinical course of these infants corresponded to those described in the literature as occurring in amyotonia congenita, whereas other aspects of their clinical course were more suggestive of the findings recorded for progressive muscular atrophy of spinal origin. The pathologic alterations, as noted above, are those described in association with either condition. The clinical and pathologic findings in these infants, then, would appear to support the view that the diseases classically referred to as amyotonia congenita and progressive muscular atrophy of spinal origin are one and the same clinical and pathologic entity. Such a concept is of more than academic interest, as the prognosis for any given patient must, if this concept be accepted, be considered as extremely grave, and the prognosis for future siblings must be guarded.

DISCUSSION

Dr. Randolph K. Byers, Boston: I think this is a very important discussion because of the prognostic implications for other members of the family. I am frequently confronted with the problem of explaining to mothers on whose first infant a diagnosis of amyotonia congenita has been made why the second child is dying of infantile muscular atrophy.

The idea of a specific entity called amyotonia congenita, which was first put forward by Oppenheim in a very poorly worked out paper with too short a follow-up and too small a number of patients, is well entrenched in the literature, and the words amyotonia congenita mean to most doctors, and to lay people who take the trouble to go to public libraries and look the subject up, that it is all right for them to have other children.

Brandt, in Denmark, looked up about 120 children on whom diagnosis of amyotonia congenita had been made, and he told us what Dr. Arey has been telling us. Of these children, a very small percentage, something like six out of the whole group, followed the course that had originally been described by Oppenheim. None of them were competent. Three or four of them had siblings without a recurrence. There is a small chance of that happening, but by and large these weak hypotonic babies have Werdnig-Hoffman's disease, which, as you know, is a very familial disease with a very high incidence of recurrence in siblings.

I think it is important to recognize that this disease can begin before birth. In many of the instances in which autopsies were obtained there were stories in which the mothers had said that they felt life up until a month before delivery and then the baby stopped moving. It can begin up to two or three years after birth. The later it begins, the less acute the course and the slower the progression. Just because of slow progression, you are not sure of the diagnosis, and certainly its presence at delivery is no evidence that it is the benign form of disease.

PAPERS READ BY TITLE

Engelmann's Disease: A Nonprogressive Familial Muscular Dystrophy with Bone Changes. Dr. Bertram R. Girdany (by invitation), Pittsburgh.

In 1929, Engelmann described a child with muscular weakness who showed characteristic roentgen changes in the skeleton. Since that time the findings on 12 similar patients have been reported in the literature. The prognosis has been considered unfavorable, and the term "progressive" diaphyseal dysplasia has been applied to the disease.

This paper reports four additional cases of Engelmann's disease. Three of these occurred in one family, with a mother, her brother, and her son affected. The mother, who shows the characteristic bone changes on roentgen examination, is now, and has been, asymptomatic and free of muscular weakness. Her brother exhibited a waddling gait similar to that reported in other patients with Engelmann's disease; at the age of 12 he was so weak that he was unable to walk distances or run. Following prolonged rigorous muscular exercises, he is now able to pursue a normal adult life and performs manual labor for his livelihood. The son shows weakness, diminution in muscle masses, roentgen changes, and a peculiar gait. He presented with clinical signs of progressive muscular dystrophy and "climbed his frame."

A fourth patient, now 11 years of age, has been followed for nine years, during which time she was becoming progressively weaker. During the past four months, as a result of physiotherapy and exercises, she has demonstrated remarkable improvement in her clinical condition.

These observations suggest that Engelmann's disease, which can be confused clinically with progressive muscular dytrophy, may be familial in nature, that it is not necessarily a progressive condition, that it is amenable to physiotherapy, and that the bone changes may be present without clinical signs of weakness.

Rh Antigenicity of Gamma Globulin: Dr. Neva M. Abelson (by invitation), Philadelphia.

Widespread use of a new therapeutic agent may be followed by unforeseen difficulties. Therefore, pediatricians have asked if increased use of gamma globulin may lead to more cases of Rh sensitization. Experiments bearing on this question have been made. Fourteen persons were sensitized to the blood antigens C and D. Their antibody titers were allowed to fall to low levels. Challenge doses of gamma globulin were administered intradermally, subcutaneously, and intramuscularly. There were no reactions, and the antibody titers did not change. Subsequent injection of 0.1 ml. of whole blood caused immediate stimulation of antibody production.

Experimental Studies on the Pathogenesis of the Nephrotic Hyperlipemia. Dr. Walter Heymann, Dr. L. W. Matthews (by invitation), and Dr. Donald B. Hackel (by invitation), Cleveland.

Nephrotoxic renal disease was induced in rats by the intravenous injection of antikidney serum from rabbits. A C^{14}-labeled emulsion of trilaurin was given by intravenous injection to 16 of these and to 15 control rats. Its utilization was determined by the amount of C^{14} in the expired CO_2. There was no correlation between trilaurin utilization and the degree of hyperlipemia in the nephrotic animals. The clearance of trilaurin and of a coconut oil emulsion from the blood stream was identical in hyperlipemic and normal rats. Subtotal hepatectomy performed in 16 rats prior to the injection of antikidney serum resulted in a statistically significant diminution of hyperlipemia as compared with 13 rats given injection of antikidney serum but not hepatectomized. Hepatectomy alone and hepatectomy followed by intravenous injection of normal rabbit serum did not change the lipid values in 14 control rats. Subtotal hepatectomy in 13 rats with well-established renal disease was temporarily followed by considerable decrease

of the hyperlipemia in all instances. Corresponding controls using sham hepatectomy and splenectomy permit the conclusion that the liver plays an important part in the development of the nephrotic hyperlipemia.

The role of the kidney was studied in the following experiments. When bilateral nephrectomy was performed just before injecting antikidney serum, the hyperlipemia was not greater after 48 hours than in control nephrectomized rats given injections of serum from untreated rabbits. When bilateral nephrectomy was performed in rats with already established nephrotoxic renal disease, the high total lipid values were markedly decreased in all rats. In eight additional rats the bilateral nephrectomy was performed in two stages. After the first kidney was removed there was a drop in total lipid in all animals after 48 hours. The second kidney was removed three to five weeks later, resulting in further decrease in blood lipid values. Unilateral nephrotic disease was successfully produced in 28 of 72 rats in which the left renal pedicle was clamped before and for 30 minutes after injection of antikidney serum. Hyperlipemia did develop in the animals with unilateral nephrotic disease. These experiments indicate that the presence of renal tissue is essential to the production and maintenance of hyperlipemia in nephrotoxic renal disease and that the presence of one normal kidney does not prevent the hyperlipemia. These results do not support the view that the nephrotic hyperlipemia is due to the absence of a blood-lipid-concentration-depressing substance. They do favor the conception of a fat-mobilizing agent produced by the nephrotic kidney.

Concerning the Importance of the Homeostatic Systems in the Recovery of Patients Requiring Parenteral Fluid Therapy. Dr. G. A. Kerrigan (by invitation), Dr. J. D. Crawford (by invitation), Dr. R. T. Sceery (by invitation), A. Heeley (by invitation), M. Terry (by invitation), and Dr. N. B. Talbot, Boston.

This paper describes the manner in which ill and depleted patients given water, dextrose, and electrolytes intravenously at physiologically tolerable rates retained and rejected these substances in accordance with their respective needs. It is shown that these persons were able to regain and maintain metabolic normalcy with considerable efficiency. The importance of the homeostatic system in accomplishing this goal is illustrated by observations on patients whose ability to retain and reject substances administered in accordance with need was impaired either by a disorder in one of the major homeostatic systems or by the administration of substances at rates which were incompatible with efficient homeostatic function. Finally, data are presented which illustrate the fact that it may be difficult by ordinary history and physical examination to diagnose accurately a patient's repair plus maintenance needs. At the same time, it is shown that this may not be of serious consequence provided one takes advantage of the homeostatic systems in planning parenteral fluid therapy.

Unsuspected Multiple Traumata to the Skeleton in Infancy and Childhood. Dr. Bertram R. Girdany (by invitation), Dr. Thomas McHenry (by invitation), Pittsburgh.

Accidents are the most frequent cause of death in preschool children and form the second most common cause of death in the infant under one year of age. Multiple traumata to the skeleton are an important cause of infant morbidity and are frequently not recognized or suspected.

Seventeen infants and children with previously unsuspected multiple traumata to the skeleton have been seen at the Children's Hospital of Pittsburgh in a two-year period. The presenting complaints included failure to do well, poor growth and development, easy bruising, malnutrition, blindness, and muscular weakness.

The differential diagnoses included blood dyscrasia, syphilis, scurvy, rickets, celiac disease, purpura, and osteogenesis imperfecta. After roentgenograms of the skeleton showed characteristic changes, direct questioning of the parents in most instances elicited the story of trauma. Social service investigation was sometimes necessary before the circumstances of repeated injury could be established.

Appropriate case reports and roentgenograms will be shown, and the differentation of this from the other conditions it simulates will be given. Multiple traumata to the skeleton should be considered in the differential diagnosis whenever poor growth and development are present without obvious cause.

Urinary Excretion of Lead in Children: Diagnostic Application. Dr. R. K. Byers, Dr. Clarence Maloof, and Margaret Cushman, M.A., Boston.

This study is an attempt to apply the excretion of lead in urine to the diagnosis of lead poisoning. Past studies have indicated that the level of lead in the blood is not a satisfactory criterion. The great variability of 24-hour urine volume in children makes it unlikely that urinary lead concentration is a reliable index.

Several methods of quantitative determination of lead in urine were studied, and the microchemical method of Fairhall has been found most reliable in our hands. Methods of collecting 24-hour urine specimens without contamination by lead were developed.

Urinary concentration of lead in the control children varied from 0 to 400 γ per liter. While and 23 persons with lead poisoning.

Urinary concentration of lead in the control children varied from 0 to 400 γ per liter. While values in the children with lead poisoning tended to lie in the higher range of concentration, there was considerable overlap, the range being from 35 to 720 γ per liter.

When the urinary excretion was reduced to a basis of micrograms per 24 hours, certain facts emerged. All of the children excreting over 80γ per 24 hours had lead poisoning; those with values between 50 and 80 γ per 24 hours had either lead poisoning or unusual exposure to lead; most of those with values below 50 γ per 24 hours did not have lead poisoning. Exceptions were three children with lead poisoning in whom circulatory failure, secondary to severe encephalitis, apparently caused renal ischemia and one child with clinical lead poisoning, with values of 24 and 28 γ per 24 hours, for which no explanation was possible.

Six children have been treated with Versene (ethylanediamineteraacetis acid tetrasodium salt), during lead poisoning. Of these, one was in extremis and died about half an hour after beginning treatment. In the others, urinary excretion of lead rose to ranges between 2,000 and 4,500 γ per 24 hours as determined by a dithizone (diphenylthiocarbazone) method for one or two days after treatment was instituted. In one, the symptoms of lead encephalitis cleared fairly rapidly. Three with anemia, vomiting, gastrointestinal complaints, and elevated spinal fluid protein values improved rapidly. Whether these children will be spared the type of mental defect previously reported by Lord and Byers will be followed with interest.

Observations over several months after treatment have shown recurrences of symptoms suggestive of lead poisoning in two children in relationship to acute infections. These have consisted of recurrences of cramps and positive coproporphyrin tests in the urine. Large amounts of lead were excreted during retreatment, a month or two after the original courses. These children appear not to have ingested further lead after their discharge. These findings strongly suggest that Versene does not remove the stored lead in the skeleton adequately and that during the year or so following the cessation of lead ingestion acute infections should be regarded as important threats to brain maturation.

The three other children resumed their habit of pica as soon as they returned home, in spite of psychiatric and social efforts. This points to the importance of the removal of all possible sources of lead from the environment of such children, either with paint remover or by finding new housing.

Application of Recent Advances in the Treatment of Tuberculous Meningitis. Dr. Douglas S. Damrosch (by invitation), Catherine Ellis, A. B. (by invitation), and Dr. Hattie E. Alexander, New York.

Even though streptomycin in conjunction with either *p*-aminosalicylic acid or thiazolsulfone (Promizole) represents an important advance in the treatment of tuberculous meningitis, it has been clear for some time that there are serious limitations of this therapy. Approximately 50% of the patients in most large series of cases have died; a significant proportion of those who survive exhibit signs of cerebral damage, and the injury from the necessarily long duration of streptomycin therapy has destroyed vestibular function in virtually all and produced reduction of hearing in a significant proportion. This paper presents the results of a therapeutic regimen which aims to correct some of these limitations. Emphasis has been placed on two aims: (1) the removal of fibrin which is believed to play a role of production of hydrocephalus and also as a protector of the tubercle bacillus against antibiotic action; intrathecally administered purified protein derivative of tuberculin (PPD) is being studied for this purpose; (2) the addition of a second powerful agent, isoniazid (isonicotinic acid hydrazide), which appears to be at least

comparable to streptomycin in its antituberculous activity and perhaps superior because of its greater action against intracellular organisms. The regimen is a plan to reduce the duration of streptomycin administration to a minimum on the premise that isoniazid and streptomycin together may work more efficiently and that effective levels of isoniazid in spinal fluid can be maintained by the oral route.

One year ago, on the basis of these aims, the following program was planned. Streptomycin is given intrathecally in doses of 25 mg. daily for only the first seven days. Administration of isoniazid and *p*-aminosalicylic acid orally and streptomycin intramuscularly is continued until the spinal fluid is normal. Alternate patients are given PPD intrathecally after the work of Cairns and Smith.

Nine patients have been treated according to the above plan with one death. This group, though still small, has shown what appears to be more dramatic clinical improvement than one would anticipate under earlier treatments. The child who died was critically ill upon admission; there was increased intracranial pressure at that time. The eight survivors have normal spinal fluid and are free of evidence of active infection.

Four of the nine patients have received intrathecally administered PPD. It is obviously too soon to draw conclusions on the efficacy of PPD; however, it has been shown that it can be used without apparent harm to the patient. PPD administration is started after one week of chemotherapy, minute doses at first and increasing rapidly until the desired reaction, fever and increase in protein and cells of spinal fluid, is reached. This reactive dose is repeated at weekly intervals for at least four weeks.

Tubercle bacilli have been grown from the spinal fluid in each case to be reported. With one exception, cultures became negative within four days. The exception occurred in one of our sickest patients to survive, a boy treated with PPD. His cultures remained positive during the first seven weeks of treatment, in spite of the fact that the organisms remained sensitive to both streptomycin and isoniazid.

Evidence will be presented to show that resistance to streptomycin is seldom the cause of failure of treatment in tuberculous meningitis. It is suggested that the protective effect of fibrin is responsible for persistence of sensitive tubercle bacilli in spinal fluid for many weeks following start of treatment or on recrudescence.

The Diagnosis and Treatment of Patent Ductus Arteriosus in Infancy. Dr. Paul Adams Jr. (by invitation), Dr. F. H. Adams (by invitation), Dr. R. L. Varco (by invitation), Dr. J. F. Dammann Jr. (by invitation), and Dr. W. H. Muller (by invitation), Minneapolis.

The typical continuous murmur of the patient ductus arteriosus may not be present in older children and adults with pulmonary hypertension or heart failure. This typical murmur is also absent in the large percentage of children with patent ductus arteriosus under one year of age. This report presents the clinical course in certain severe cases of patent ductus arteriosus and emphasizes that early diagnosis and surgical correction are possible and highly desirable in certain severe cases.

The cases of 16 patients under 18 months of age are reviewed in which the diagnosis of patent ductus arteriosus was established and surgical correction undertaken.

Eleven of the patients had severe and repeated upper respiratory infections and/or pneumonia. Failure to gain weight was a common symptom. On physical examination growth retardation was very marked in 11 of the patients. Eleven patients under one year of age had only a systolic murmur and did not have the typical continuous murmur of the patent ductus arteriosus. This systolic murmur was maximum at the apex in four patients and over the pulmonary area in the remainder. There were seven patients aged 12 to 18 months, and six of these patients had the typical continuous murmur in the pulmonary area.

X-ray examination revealed the following findings almost uniformly: an enlarged heart, an increased pulmonary artery segment, increased root shadows and pulmonary vascular markings, and an enlarged left atrium.

The electrocardiogram showed normal or right axis deviation in all cases. On unipolar leads seven patients had left ventricular hypertrophy, and in six of these there was associated right ventricular hypertrophy. No patients had right ventricular hypertrophy as an isolated finding.

Heart catheterization and retrograde aortography were used to establish the diagnosis when clinical findings were inconclusive. In those patients catheterized the oxygen content was 1.4 vol.% increased in the pulmonary artery over the value in the right ventricle. The pulmonary artery pressure was moderately elevated in all patients.

There was only one fatality at surgery, and that patient's lesion was found at postmortem examination to be complicated by endocardial fibroelastosis of the left atrium, left ventricle, and mitral valve. The ductus was found in all cases to be relatively larger than in older children, approaching or equalling the aorta in size. Although a systolic murmur persisted in six patients following surgery, the murmur appeared to be functional in all except one case. Although the increase in rate of growth was variable in the group as a whole, the only four patients who were followed longer than one year all had returned to their expected auxodrome.

The importance of patent ductus arteriosus as a cause of death in infancy has been recorded to be as high as 25% in some series. This is a difficult fact to establish because pathologists usually consider this as a normal finding in infancy regardless of its size in relation to the aorta.

Increase in rate of growth following surgery is variable, many patients recovering their expected growth rate by one and one-half years. Failure to experience improved growth rate may be due to (1) constitutional growth impairment; (2) persistent cardiovascular anomalies or pulmonary pathology secondary to pulmonary hypertension.

Further studies, such as cardiac catheterization or retrograde aortography, are necessary to establish the diagnosis in the absence of the characteristic physical findings of a continuous murmur. These studies are indicated in those infants who have manifest heart disease (cardiomegaly, dyspnea, peripheral edema) and in whom the diagnosis is not obvious after using the routine methods of study and examination.

Intussusception: A Review of One Hundred Seventy-Two Cases with Comparison of Results of Treatment by Hydrostatic Pressure and by Surgery. Dr. Lee Weil Bass (by invitation) and Dr. Bertram R. Girdany (by invitation), Pittsburgh.

During the past 25 years, 172 patients with intussusception have been treated at the Children's Hospital of Pittsburgh. There have been 32 deaths, 18.6% mortality rate. In infants under 10 month of age, there have been 112 cases, 26 deaths, 23.2% mortality rate. In infants over 10 months of age, there have been 60 cases, 6 deaths, 10.0% mortality rate.

The monthly incidence shows a peak in July and August. There were approximately two times as many boys as girls. The duration of symptoms preceding treatment was directly related to survival; the mortality rate rose from 14.6% on the first day to 28.5% on the fifth day. The following offered bad prognosis: history of cathartic administration, temperature greater than 101 F., abdominal distention, palpable rectal mass, prostration, dehydration, and peritonitis, with increasing mortality rates in that order. Fifteen of 30 patients with peritonitis died. Fourteen, or 8.1%, of the 172 patients showed demonstrable lead points.

Prior to 1950, all patients with intussusception were treated surgically. Since that time, hydrostatic pressure with barium enema under fluoroscopic control has been used routinely as the initial treatment. There have been 28 patients so treated; in four instances surgery was necessary to complete reduction.

The indications for treatment were the same regardless of therapy used. Dehydration, marked anemia, or shock is corrected before therapy is started. Lengthy duration of symptoms is not a contraindication for hydrostatic pressure therapy. Eight cases of greater than 48 hours' duration, including one of 8 days' and one of 9 days' duration, were completely reduced with hydrostatic pressure.

Morbidity studies show significant differences following reduction by hydrostatic pressure and reduction by operation. Temperature elevation following the hydrostatic procedure is uncommon. The average hospital stay following hydrostatic reduction was 2.5 days; the average following surgical reduction was 12.5 days. Four patients were returned home immediately following reduction by hydrostatic pressure. All patients who had hydrostatic reduction of intussusception began oral feeding within 24 hours after the procedure.

One hundred forty-three patients were treated by surgery alone with 26 deaths (18.2%). From 1946 through 1950, 39 patients were treated by surgery, with four deaths (10.2%). During the following two years, 24 patients with intussusception had complete reduction by hydrostatic means, with one death (4.15%).

The mortality rate observed following reduction of intussusception by hydrostatic pressure compares favorably with the mortality rate following surgical reduction. The advantages in terms of patient morbidity following hydrostatic-pressure reduction are discussed.

The Prophylaxis and Treatment of Bacterial Complications of Measles. Dr. Samuel Karelitz, Dr. Zacharias E. Matthews (by invitation), and Dr. Charles Chi Chiang (by invitation), New York.

Attempts to treat measles with sulfonamides and antibiotics have been completely unsuccessful in the sense that the disease per se was not influenced. The rash, Koplik spots, and communicability of the disease were not altered. Nevertheless, the measles patients with either penicillin or chlortetracycline (aureomycin) did derive definite benefit from the antibiotic therapy. The temperature was below 100 F. about two days before that of the untreated controls. The bacterial diseases, otitis media, pneumonia, etc., complicating the measles were either prevented or cured as compared to an incidence of about 23% in the controls. Treatment consisted of four daily injections of 300,000 units of aqueous penicillin procaine, chlortetracycline per os for four days, 50 mg. per kilogram of body weight per day.

single injection of 600,000 units for children up to 5 years of age and one of 1,200,000 units for single injection of 600,000 units for children up to 5 years of age and one of 1,200,000 units for children over 5 years might duplicate the beneficial effect derived from the four-day penicillin or chlortetracycline treatment. Fifty children, on admission to the Willard Parker Hospital with measles, were given a single intramuscular injection of Benzethacil (dibenzylethylenediamine-dipenicillin G) in the dosage indicated. Fifty children were given daily injections of 300,000 units of aqueous penicillin procaine intramuscularly, and 50 were given no antibiotic therapy unless complications developed. Alternating cases were divided into these three categories. All were encountered during December, 1952, and January and February of 1953.

The results with the single dose of Benzethacil were similar to those observed after daily injections of aqueous penicillin procaine and in sharp contrast to the untreated controls. There were no manifest bacterial complications in either treated group, while among the controls otitis media or pneumonia developed in some and several other patients were so ill that we feared omitting therapy and penicillin was introduced.

The treated group had a shorter febrile course than the controls.

Since Benzethacil was irritating and caused considerable discomfort to the patient at the injection site, another group of 50 patients are receiving larger doses of aqueous penicillin procaine intramuscularly at two-day intervals, 600,000 to 1,200,000 units for children up to 5 years and over 5 years, respectively. Too few of the latter group have been observed to date to justify a conclusion.

Much of the available gamma globulin is being diverted for the prophylaxis of poliomyelitis. It is therefore possible that less of it will be available for use in measles prophylaxis. The fact that antibiotics are effective in preventing bacterial complications is therefore currently very important.

We do not wish to imply that prophylaxis with gamma globulin or a substitute can be replaced by antibiotics. The disease is very much milder, shorter, and almost entirely devoid of complications, including encephalopathy, after modification with gamma globulin or convalescent serum, whereas the antibiotics are beneficial only in eliminating bacterial complications.

A New Technique for Transfusion of Infants and Children with the Use of Plastic Equipment. Dr. Leonard Apt (by invitation), Dr. Louis K. Diamond, and Dr. Eric J. Wake (by invitation), Boston.

The use of plastic equipment for the collection, storage, and infusion of blood has been developed recently by C. Walter. To meet the special needs in infants and small children in a simple manner, the technique and equipment have had to be modified and elaborated.

Blood is collected into a plastic bag containing anticoagulant acid citrate solution. The bag, plastic donor tube, and a laminar flow phlebotomy needle are in one piece. The bag of blood is hermetically sealed by applying a radio-frequency sealer across the proximal end of the donor tube. Segments of donor tube containing blood can be sealed off to serve as pilot tubes. The bag is suspended from a metal stand and stored at 4 C.

Inasmuch as the majority of units of blood used for infants and children are less than 500 ml., two additional bag sizes were made available—250 ml. and 150 ml. Attached to each of the smaller bags is a segment of plastic tubing with a coupler at the end for insertion into the delivery tube of the 500 ml. bag of blood. The blood is transferred by gravity. The smaller bag rests on a scale so that the amount of blood desired may be obtained.

The plastic recipient set is in one piece and consists of a combination filter and drip chamber, a piercing coupler, and a short side arm of tubing connected by a plastic Y coupler near the needle end of the set. The side-arm attachment may function as a three-way stopcock.

There are many advantages of the equipment. It is a completely closed system during the collection, transfer, and administration of blood. It is hemorepellent throughout. Thus, there is delayed coagulation and less rapid degradation of shed blood. There is no liquid-gas interface. The equipment is inexpensive, light, nonbreakable, and collapsible.

It has been demonstrated that the erythrocytes collected and stored in plastic equipment and those handled in glass bottles have similar post-transfusion survival characteristics. When the standard glass-bottle equipment is used, small units of blood are prepared by transfer with the use of suction. In order to determine whether this has a detrimental effect on the erythrocytes, the viability, estimated from the osmotic fragility test (described by Gibson and co-workers) was determined on blood before and after transfer. Similar tests were performed with blood in the plastic system where transfer is by gravity. There was no significant alteration in the estimated survival of the transferred erythrocytes in either system. The hemoglobin concentration in the supernatant plasma likewise failed to show an appreciable change.

Pediatric Discussions with Parent Groups. Dr. Barbara Korsch (by invitation), Dr. Lewis Fraad (by invitation), and Dr. Henry L. Barnett, New York.

For several years, pediatric discussions have been held with parent groups at The New York Hospital–Cornell Medical Center. These have included single group discussions with either fathers or mothers of newborn infants and several series of four or five evening meetings each with parents of children with nephrosis or diabetes mellitus.

Since the psychiatric training of the pediatricians who led these discussions was limited, their function was not that of group psychotherapists. In the groups, as in their individual relationships with parents, the pediatricians served both as medical authorities and as physicians with whom the parents could work through some of their feelings about their sick children, their handling of the children, and their relationship to the medical personnel.

The group meetings were utilized extensively by the parents to learn more about their children's conditions. The pediatricians believed that it was important for parents of children with chronic illness, such as diabetes and nephrosis, to understand as much as possible about the natural history of the disease, the rationale of diagnostic and therapeutic measures, the relative significance of symptoms, signs, and laboratory examinations, and the essential problems in management. Emphasis was placed on helping the parents to feel so secure in their understanding of the disease that they could handle the nonmedical advice to which they were constantly subjected.

The pediatricians were impressed that the parents in the groups were able to grasp clearly the complex subjects discussed. It was thought their intensive interest compensated in part for their lack of background information and enabled them to understand complicated technical discussions.

Many reactions of the parents appeared to be referable to the group approach: reassurance of some parents by other parents undergoing or having passed through similar experiences; verbalizations of guilt relating to the child's illness and seeing these in the perspective of the expressed feelings of other parents; learning techniques and insight in relation to the home care of the patient. Anticipatory guidance, as practiced customarily by pediatricians, appeared to occur spontaneously within the group of parents. In addition, they were able to express hostility against some of the medical authorities and resentment toward some of the experiences in the hospital or the clinic or with individual physicians. It seems beneficial to bring such negative feelings into the open and constructive suggestions for improvement in hospital routines were proposed and carried out as a result of the discussions.

For the pediatricians, these experiences were of specific educational value. They provided new insights into general child behavior, into the reaction of both children and parents to illness, into the problems of caring for the sick child in the home, and into their own role in relation to children and parents at home and in the hospital.

In the presentation, specific examples will be given to illustrate the areas where this approach appeared to be of value to parents and staff. Suggestions will be made concerning some of the criteria to be considered in selecting the groups, selecting the leaders, and conducting the discussions. Finally, possible hazards and disadvantages of this method as observed or anticipated will be pointed out.

Observations in Chronic Nephrotoxic Serum Disease in Rats Utilizing Renal Biopsy and Electron Microscopy. Dr. Carolyn F. Piel (by invitation), Dr. F. W. S. Modern (by invitation), and Richard F. Baker, Ph.D., San Francisco.

The renal disease produced in rats by injection of anti-rat-kidney serum prepared in rabbits has been described as closely resembling the nephrotic syndrome observed in children. In the human disease, clinical observations and tests of renal function have not yet been correlated with the pathologic lesions until evidence of progressive renal failure occurs. In this stage of the disease, the histologic glomerular lesion is indistinguishable from that of chronic glomerular nephritis. The renal disease of children who die during the course of the nephrotic syndrome from causes other than renal failure is characterized by fibrinoid degeneration and collagenization of the basement membrane. The relationship of nephritis to nephrotic change is unknown, as biopsy material in individual cases is limited.

In a recent study of the acute phase (first two weeks) of the experimental disease, it was found that two types of disease could be distinguished clinically and pathologically: one, "nephritic," the other, "nephrotic." The initial type of response depended in part apparently on the potency of the nephrotoxic serum.

These observations have been extended using mucopolysaccharide and other modern stains for standard histologic techniques and comparative sections for electron microscopic study. The natural course of the pathologic lesion has been followed by periodic renal biopsy and serial killing of animals. With electron microscopy, minute glomerular alterations as well as changes in brush border and cytoplasm of tubular cells have been demonstrated. Slides illustrating development of the renal pathology from acute to chronic stages of the disease will be presented with comparable light and electron microscopic sections.

The Developing Fundus Oculi of the Premature Infant and Its Relationship to Retrolental Fibroplasia. Dr. Mary Critz Fletcher (by invitation), Houston, Texas.

The development of the eyes of 320 premature infants, most of whom have weighed less than 1,700 gm. at birth, has been followed over a three-year period. Very small premature babies are born with an immature fundus which passes through a transitional stage before reaching the mature fundus similar to that of the full-term infant. After maturation has been reached, the eye may remain normal or may progress on to show the early changes of retrolental fibroplasia. The early changes, in turn, may reverse spontaneously or may progress to the severe stages of the disease with varying degrees of visual impairment.

Of the 320 infants examined, 86 had retrolental fibroplasia, in 38 of whom massive retinal edema developed with detached retinae and malignant hemorrhages. There was a statistically significant increased incidence of retrolental fibroplasia in the white boy babies, which may possibly be related to a greater immaturity and poorer survival rate. It is also significant that the smallest infants and those with the most immature fundi at birth are the ones in whom severe retrolental fibroplasia with its resulting blindness is most apt to develop. Evidence is presented to show that the small premature infant and those infants with severe retrolental fibroplasia have a high and fluctuating myopia, which may remain as a residual lesion.

The parts played by (1) relaxed tone of blood vessel walls, (2) increased arterial tension, and (3) decreased peripheral resistance in the pathogenesis of the early stages of retrolental fibroplasia were considered critically. It could not be demonstrated, within the limits of this study, that they were of significance. The role of excessive oxygen administration and rapid changes of

oxygen environment in relation to hypervascularity were discussed. From the observation reported herein, the disease, retrolental fibroplasia, appears to result from an as yet unknown factor or series of unknown factors, affecting an immature eye which is passing through a period of critical differentiation and maturation.

Striae: A Common Finding in Normal Adolescent Children. Dr. Warren R. Sisson (by invitation), Boston.

Pink striae were frequently observed in the course of growth study of normal adolescent children.

Reference to striae in the adolescent period in the literature is noteworthy for its absence. In the standard treatise on growth and development and, particularly, on adolescence, striae have not been commonly associated with the adolescent period.

As striae were found so frequently in adolescence, three studies were outlined, the first of which is presented here. This consists of a study of 200 normal adolescent children, ages 10 to 16, who were observed consecutively for a period of one to three years. They were studied with special reference to the instance of striae, their appearance, their location, their change in color, and their correlation with other well-recognized objective signs of adolescent development, including obesity and acne.

In this group of 200 children, 65, or 30%, exhibited striae. In the group there were 89 boys and 111 girls; 42.3% of the girls and 19.1% of the boys showed striae. The highest instance of striae occurred in girls between the ages of 12 and 13 years.

The striae were similar to the linear markings seen in pregnant women and in Cushing's syndrome.

The colored striae were located most frequently over the upper thigh, involving the gluteal region. The distribution varied considerably, and frequently only a few striae were noted at the time of observation. The striae were, in general, bilaterally distributed. In their early stages they were frequently elevated.

The striae were associated with other developmental findings, such as pubic and axillary hair, development of breasts, external genitalia in the males, acne, and the menarche. It has been noted that striae occur in all stages of adolescence and are more frequent in the girls between the ages of 12 and 13, when all the usual characteristics of adolescence are in their third or adult stage. In boys the highest incidence is a year or two later.

We have shown by following children with pink striae that over a period these become white.

Striae were noted more frequently in obese children than nonobese children, but they were frequently found in both boys and girls with no excess of adipose tissue. Striae were not always seen in so-called obese children. In the group of 200 children, 48 were considered to be obese; 29, or 60%, of these showed typical striae. Among the 48 obese children, 32 were girls and 16 were boys.

Striae were found frequently in adolescents who had severe acne.

From these observations it would seem that striae were a very common finding in the adolescent period, both in boys and girls. They occur more frequently in adolescent obese girls, but they are found in boys and girls who have or never have had any excess of subcutaneous fat. It would seem, therefore, that obesity per se was not the only cause for these linear markings called striae. There is some evidence to suggest that striae occur in areas of the body where the skin is under greatest tension. Although no determinations of steroid activity have been made in this group, it would seem that the striae of adolescence occur in a period where steriod activity is increased.

Studies in Sickle-Cell Anemia: Effect of Age (Maturation) on Incidence of the Sickling Phenomenon. Dr. Roland B. Scott and Dr. Lulabelle C. Freeman (by invitation), Washington, D. C.

Clinical manifestations of sickle-cell anemia are rare before the age of 6 months. Likewise, the asymptomatic sickling trait is less commonly found in early infancy. In a previous study we found that 3.4% of 262 newborn Negro infants showed the sickling phenomenon, but none had clinical evidence of sickle-cell anemia. Sickling was demonstrated in 7.6%, or 209, older children. Two of these older subjects had clinical manifestations of sickle-cell disease. It was, therefore,

postulated that maturation has some effect on the appearance of the sickling phenomenon and that we might expect to find an increasing incidence of sickling from infancy throughout childhood. The present study was undertaken to test this hypothesis.

Blood studies were performed on 1,100 Negro children aged 1 month to 16 years, taken at random.

Methods.—Hemoglobin determinations (colorimetric method) and sickling tests (bisulfite method) were done on all subjects. In addition, those who showed sickling had the following procedures: quantitative serum bilirubin, alkali denaturation of hemoglobin, reticulocyte count, blood smear for sickling (Wright's stain), and a history concerning symptoms or previous diagnosis of sickle-cell anemia. When available, the parents were tested for sickling.

Criteria for Differential Diagnosis between Trait and Sickle-Cell Anemia.—The following criteria were used for the diagnosis of sickle-cell anemia:

1. Anemia (erythrocyte count below 3,500,000 per cubic millimeter and/or hemoglobin below 10 gm.)
2. Sickling of erythrocytes
3. Evidence of hemolysis of erythrocytes
4. Clinical picture of sickle-cell anemia
5. Alkali-denatured hemoglobin (above 1.7% in children over 2 years of age). In a number of cases with borderline values this criterion could not be applied.

Comparative Incidence of the Asymptomatic Sickling Trait (Sickle-Cell Anemia Excluded) in the Two Sexes

	Boys				Girls			
	No. Normal and Sickling	Sickling	%		No. Normal and Sickling	Sickling	%	
1 mo. 4 yr.	345	17	4.92	±0.90	242	15	6.19	±1.55
5 yr.-16 yr.	290	23	7.93	±1.16	201	5	2.48	±1.09
Total	635	40	6.29	±1.58	443	20	4.51	±0.98

Results.—The survey disclosed 22 cases of sickle-cell anemia and 60 subjects bearing only the asymptomatic sickling trait. Inspection of the data fails to show a significant effect of age on the expression of the sickling phenomenon, except in the newborn period.

Sixteen cases of sickle-cell anemia in boys and six cases in girls were encountered in the total test group comprising 651 boys and 449 girls.

The comparative incidence of the asymptomatic sickling trait (sickle-cell anemia excluded) in the two sexes is shown in the Table.

Evaluation of Routine Serial Fluoroscopic Examination of the Heart with Special Reference to Angle of Clearance of the Left Ventricle. Dr. May G. Wilson, Dr. Nathan Epstein (by invitation), Dr. Helen N. Helper (by invitation), and Dr. Katherine Hain, New York.

The clinical importance of fluoroscopic examination of the heart in the frontal and oblique views to detect abnormality of the individual chambers is now established. It is not as well recognized that serial fluoroscopic examinations at specific degrees of rotation afford an opportunity for early detection of slight degrees of chamber enlargement. This is particularly important for early diagnosis of heart disease in children.

Continuous medical supervision of 500 children during the past 15 years, the majority of whom were observed from birth, provided data for determining the normal variations in 3,000 routine serial fluoroscopic examinations. These were made at least annually by 35 examiners, with an average of 4 different observers for each child.

The variations in the cardiac silhouette in posteroanterior and oblique views due to position of the heart, posture of the patient, and errors in technique were surprisingly low. Increased saliency of the pulmonary segment in the posteroanterior view occurred in 1% of the fluoroscopic examinations and retro displacement of the esophagus in the right antero-oblique view was also noted in 1%. The angle of clearance of the left ventricle was 55 degrees or more in only 10% of the fluoroscopic examinations.

For comparison, 1,000 serial fluoroscopic examinations of 100 children with rheumatic heart disease were reviewed. It was found that in 100% of the fluoroscopic examinations the left ventricle cleared the spine at 55 degrees or more in the left antero-oblique position. In 26 of these children in whom rheumatic fever developed while under observation, the angle of clearance of the left ventricle increased from a previous normal value of 50 degrees to 55 to 60 degrees. These observations confirm the validity of the angle of clearance of the left ventricle as an early index of left ventricular enlargement.

It is concluded that routine fluoroscopic examination of the heart in the posteroanterior and oblique views at specific degrees of rotation offers a practical, economical, and reasonably accurate method for early recognition of cardiac chamber abnormality.

A Study of the Absorption of Boron Through the Normal and Denuded Skin of Infants. Douglas E. Johnstone (by invitation), Nehmie Bascila (by invitation), and Dr. Jerome Glaser (by invitation), Rochester, N. Y.

The purpose of this study was to establish the normal blood and urine boron levels in infants and children not receiving any baby powder compared to similar levels in those children with intact, as well as denuded, skin while receiving daily applications of a common commercially available baby powder containing 5% boric acid.

Weekly blood and urine boron levels were determined for five consecutive weeks on eight infants ranging in age from 9 months to 4 years. A commercially available baby powder, which had been specially analyzed for its boron content, was then applied liberally five times daily. The average application dose was determined by before and after weighing of the powder cans. Blood and urine boron levels were then determined on these same children for the next six weeks. Special boron-free glassware was used in making these collections and determinations. The results of these determinations will be presented.

Similar studies were done on infants with varying areas of denuded skin (diaper rash, burns, etc.). The results of these studies will be presented. In brief, they will demonstrate that the generally used commercial baby powders do not constitute a boric acid hazard unless large areas of skin are denuded.

An Analysis of the Factors Relating to the Maintenance of Hematopoietic Equilibrium in Chronic Anemias. Dr. Carl H. Smith, Dr. Irving Schulman (by invitation), and Dr. Gertrude Stern (by invitation), New York.

Long-term observations of children with chronic anemias receiving blood transfusions at regular intervals reveal a failure to maintain improved hemoglobin and red blood cell levels for any appreciable period. The rapid drop to pretransfusion levels accounts in large measure for divergent opinions concerning the blood levels for which transfusion is required, the amount of blood which should be administered, and the optimal intervals between transfusions. Growing concern with the possible development of hemosiderosis and hemochromatosis from the additive effects of multiple injections of blood has in recent years prompted a more conservative policy with regard to the spacing of transfusions.

In an attempt to evaluate the factor determining the variable response to transfusion in chronic anemias, studies were performed which were designed to measure quantitative aspects of hematopoiesis and erythrocyte destruction in children requiring long-term transfusion therapy. Special reference was directed to the effect of the spleen and to the effect of transfusion itself in depressing intrinsic hematopoiesis.

In a group of patients with Mediterranean anemia, sickle-cell anemia, and aregenerative anemia, serial measurements of blood volume, red blood cell mass, and hemoglobin mass were made with Evans blue dye. In addition, by use of the Ashby technique of differential agglutina-

tion, it was possible to distinguish between donor and recipient blood and thus obtain a measure of a patient's state of hematopoiesis. The data thus far indicate that several mechanisms may combine to produce suboptimal response to repeated transfusions:

1. Long-term transfusion therapy may lead to the development of decreased survival of transfused normal cells. This appears to be a function of altered splenic structure and is improved by splenectomy.

2. In chronic anemias, transfusion itself may induce depression of the patient's own level of red blood cells and hemoglobin synthesis even though continued severe anemia persists.

3. In five patients with Mediterranean anemia, hemoglobin concentrations following splenectomy were maintained at higher levels despite considerable decreased transfusions than in the preoperative period. The various factors responsible for improvement will be discussed.

The above studies indicate a need for reevaluation of the principles involved in the care of children with chronic anemia. In addition, the need for considering the possible depressant effects of transfusion therapy on hematopoiesis in many childhood disorders is indicated.

Home Treatment of Beta Hemolytic Streptococcus Infections. BURTIS B. BREESE JR. (by invitation), Rochester, N. Y.

Over 1,200 streptococcal infections were treated in the home by various methods of therapy. These divisions were, broadly, (1) symptomatic, (2) sulfonamides, (3) chlortetracycline (aureomycin), (4) penicillin. By far the largest group of infections was treated by penicillin.

Treatment results were judged by (1) the immediate clinical response, (2) the bacteriological response, (3) the recurrence rate, (4) effect on sedimentation rate, (5) effect on antibody response, (6) the incidence of late complications, namely, acute glomerulonephritis and rheumatic fever.

In practically all categories chlortetracycline and penicillin treatment were preferable to sulfonamide or symptomatic treatment. In the immediate clinical response, there was little difference in those treated with penicillin and those treated with chlortetracycline. However, in the number of recurrences, complications, and bacteriologic cures, penicillin therapy was preferable to that of chlortetracycline.

Of the various methods of penicillin treatment which were used, short periods of therapy gave poorer results than periods of therapy in which blood levels were maintained for a week or more. The patients in a considerable series of cases were treated by the new penicillin preparation, dibenzylethylenediamine-dipenicillin G in aqueous suspension (Bicillin Injection) which gives detectable blood levels for 10 days or more. This preparation injected in a single dose of 600,000 units seemed adequate to cure the vast majority of children with streptococcal infections. Of all forms of therapy used, it was least likely to be followed by either clinical or bacteriologic relapse and proved the best drug for treatment of patients in the home.

The incidence for rheumatic fever in the entire series was less than 0.1%. There was only one unquestioned case of the disease which appeared. This child was treated with a sulfonamide. Five cases of nephritis were found in the series, and in only one of these did the patient receive adequate penicillin treatment. It is entirely likely that his attack of nephritis followed the reinfection.

Observations on the Use of Cow's-Milk Substitutes in Infancy with Special Reference to the Subsequent Development of Allergic Disease. DR. DOUGLAS E. JOHNSTONE (by invitation) and DR. JEROME GLASER (by invitation), Rochester, N. Y.

The purpose of this study was to determine if it is possible to decrease the normal incidence of major allergic disease in potentially allergic children compared to their siblings and another nonrelated control group by withholding milk completely from their diets throughout most of their first year of life. Clinical data from three groups of children were compared. The experimental group consisted of 91 children who were the siblings or offspring of one or more persons with major allergic disease.

Cow's milk and beef were completely withheld from their diets from the first day of life through the first six to nine months of life. They were followed for varying lengths of time, most of them from 3 to 10 years of life. Their 70 siblings comprised the first control group. The third group consisted of a nonrelated control group of 175 children whose allergic parental

and sibling history exactly duplicated that of their counterpart in the experimental group. To obtain this number of nonrelated controls whose allergic family history exactly duplicated that of the experimental group, the allergic hereditary histories of 4,710 persons from 1,215 families were reviewed. The incidence of major allergic disease in the siblings and nonrelated groups was not included in the Table unless their allergic manifestations occurred before the present age of their counterpart in the experimental group.

From the data in the Table it may be seen that complete withholding of cow's-milk from the diets of potentially allergic infants not only decreases the incidence of eczema and cow's milk allergy but significantly decreases the allergic sequelae to these common disorders in potentially allergic children. Since McKinney and others have shown that in 60 to 80% of infants in whom eczema develops major respiratory allergy (asthma, hay fever or perennial allergic rhinitis) will ultimately develop, anything which can possibly influence the incidence of eczema and its terrible sequelae merits serious consideration.

The broad implications of these findings suggest the need for emphasizing the importance of considering the immunological development as well as the physical development of infants in

Results of Study

	Experimental Group Fed Soy Bean Milk from Birth to 9 Mo.	Siblings	Nonrelated Control Group
Incidence of major allergy	14/91 (14%)	41/65 (64%)	91/175 (52%)
Incidence of eczema	7/91 (8%)	21/65 (32%)	50/175 (29%)
Allergic sequelae to eczema	1/7—asthma at 3 yr. 6/7—still O.K. at 6 yr.	10/21—asthma by 4 yr. 4/21—hay fever by 6 yr. 1/21—P.A.R.* at 5 yr. 6/21—still O.K. at 6 yr.	24/50—asthma by 5 yr. 6/50—hay fever by 5 yr. 20/50—O.K. by 6 yr.
Incidence of cow's-milk allergy	6/91 (7%)	24/65 (37%)	53/175 (30%)
Allergic sequelae to cow's-milk allergy	All O.K. at 6 yr.	11—asthma at 6 yr. 4—hay fever at 5 yr. 1—P.A.R.* 6—chronic ezema	24/53—asthma 5/53—hay fever 1/53—P.A.R. & hay fever

* P.A.R. indicates perennial allergic rhinitis.

handling the routine pediatric care of potentially allergic children. The need for similarly withholding other common allergic offenders, such as egg, wheat, spinach, and some citrus fruits, in these children will also be discussed.

Group Discussions with Parents of Ill Children. DR. LUIGI LUZZATTI (by invitation) and BARBARA DITTMANN (by invitation), Oakland, Calif.

A few specific problems confront any pediatrician giving care to children with chronic illnesses besides those of the immediate care of the disease; some of these are as follows: (*a*) the need for all the members of the family to have accurate information and understanding about the disease; (*b*) the need for finding ways to release parental anxiety; (*c*) the need for fostering a healthy parent-child relationship when additional stress is created by the existing illness; (*d*) the need for the parents and patients to overcome the feeling that they are "different"; (*e*) the need for the parents and patients to overcome the lack of understanding and acceptance of a particular disease by the community at large.

The ordinary one-to-one approach to patients and parents in a doctor's office or clinic fulfills a need but has several limitations. It is geared to a direct approach and individual management of the case; it is limited in time, and thus the amount of information given is limited; it does not lend itself to widening the parents' focus of attention to a larger area involving the totality of the child with a disease in his family setting; it is not conducive to allaying parental anxieties with the minimum expenditure of time and energy; it emphasizes the individual case and tends to forget the elements that are common to all children with a given disease and their parents. Among the chronic illnesses juvenile diabetes is one where such deficiencies are very evident.

Thus, group discussions with parents of diabetic children were set up as a part of the services offered in the metabolic clinic of Children's Hospital of the East Bay. More recently, group discussions with selected parents of children with cerebral palsy were started. This is another condition in which the one-to-one approach is conspicuously inadequate.

In order to have proper continuity of care, it seems essential that the professional leaders of the group be the same ones that see the children individually and that the medical management of such children be the same.

The patterns of such group discussions will be outlined and some points in their content discussed. An attempt will be made to evaluate how such group discussions may help in solving the problems outlined.

Oxalosis. HENRY G. DUNN, M.B. (by invitation), New York.

This is a report on a case of oxalosis. The patient was a girl who first had hematuria at the age of 3 years and who was found to have a urinary infection and bilateral hydronephrosis with multiple renal and ureteric calculi at 5 years. After surgical removal of her calculi new ones continued to form, and the urinary infection resisted chemotherapy. Her renal function gradually became impaired. At 13 years she suffered two fractures after slight trauma, and x-ray examination showed generalized osteoporosis with osteitis fibrosa cystica, as well as nephrocalcinosis and nephrolithiasis. Neck exploration was performed, and the parathyroids were found to be normal. The patient finally died from renal failure at the age of 15 years 10 months. At autopsy the renal pelves and calyces were full of calculi consisting of calcium oxalate with an admixture of protein. The renal parenchyma showed extensive deposits of crystalline material as well as nephrocalcinosis and pyelonephritis. Large deposits of similar crystals were found partly replacing marrow in the bones, and a few clusters were present in the myocardium, pancreas, and thyroid. On analysis by chemical, optical, and x-ray diffraction methods the crystals were demonstrated to consist of calcium oxalate monohydrate.

Previously reported cases of oxalosis are summarized, and the nature of the metabolic defect is discussed.

SOCIETY FOR PEDIATRIC RESEARCH

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Twenty-Third Annual Meeting, Atlantic City, N. J., May 4, 5, and 6, 1953

Third Session

Wednesday, May 6

(Concluded from Page 515)

A Labile Fraction of Muscle Potassium. DR. MALCOLM A. HOLLIDAY, Indianapolis, DR. WILLIAM M. WALLACE, Cleveland, and DR. JAMES L. GAMBLE, Boston.

Balance studies obtained from infants on various levels of potassium intake and during changes of intake have demonstrated an irregular curve of potassium retention heretofore ascribed to variation in the volume of intracellular fluid.

An alternate explanation would be a fluctuation in the intracellular concentration of potassium without change in intracellular volume. To test this latter hypothesis the following studies were carried out.

Serum and muscle analyses were obtained on a group of normal male adult rats maintained on a standard diet of high sodium and postassium content. The intracellular concentration of potassium varied from 146 to 172 mM. per liter, indicating a range considerably greater than that of extracellular sodium concentration and not compensated by inverse changes in other cellular cations.

Additional rats were placed on a diet low in sodium and potassium. Urine excretion of potassium was negligible after two days. Groups were then killed at 3, 6, and 27 days; serum and muscle analyses were obtained. In three days, the muscle potassium was 15% less than in the group on the standard diet. Thereafter the decrease was slight.

The increase in muscle sodium described in potassium deficiency was not observed in these animals. However, when animals prepared on this diet were subjected to measures producing potassium deficiency, the replacement of further losses of intracellular potassium by sodium was equimolar, thus preserving the total base concentration of the control low-potassium group.

The data suggest the presence of a highly labile fraction of potassium in cells, which plays an ill-defined role and further complicates the already difficult interpretation of balance data.

DISCUSSION

DR. ROBERT COOKE, New Haven, Conn.: I think it would be more appropriate if Dr. Darrow led off, in that he demonstrated something comparable to the labile fraction of potassium a number of years ago in conjunction with Dr. Herbert Miller. In these experiments, animals were loaded with large amounts of potassium, and marked changes in muscle potassium were produced over a period of days.

There seemed to be some rebound, for even after large loads of potassium the muscle potassium fell to levels of 42 mM. per 100 gm. of fat-free solids, a drop comparable to what Dr. Holliday has demonstrated.

It seems surprising that rats which are simply not given potassium lose 4 to 5 mEq. per kilogram of body weight in two days. I should like to ask how much of this potassium was actually recovered in the urine.

Next, I should like to know if he has any idea as to what anion was excreted with the potassium during those periods of development of potassium deficiency.

We have produced a similar fall in muscle potassium by acute loading with sodium bicarbonate. I should like to suggest that this labile potassium which has been assumed to be of relatively little functional importance may have a good deal of significance in the ability of the animal to resist alkalosis. If one administers a large load of sodium bicarbonate, one finds that potassium makes up one-third of the fixed-cation excretion in excess of fixed anion. If the animal has his labile potassium removed by the previous administration of sodium bicarbonate, the cation excretion in excess of anion is limited after a second load.

In regard to the retention of potassium on cow's milk, in New Haven either the cows are of a different character or our balance studies are performed somewhat differently, because we can demonstrate no excessive retention of potassium on cow's-milk feedings. When potassium intake is reduced as on human milk, potassium retention remains approximately the same.

DR. LYTT GARDNER, Syracuse, N. Y.: Dr. Gilbert Mudge has demonstrated, using K^{42}, that during anaerobic incubation 45% of the K in the tissue is nonexchangeable (*Journal-Lancet* **73**:166 [May] 1953).

I wonder if Dr. Holliday would say something about this phenomenon.

DR. WILLIAM M. WALLACE, Cleveland: I might make one more attempt to get Dr. Darrow into this discussion. I think that probably one of the most significant things that occurs in potassium deficiency is the accumulation of hydrogen ions within the intracellular compartment with reciprocal decrease in hydrogen ion concentration in the extracellular fluid. The hydrogen ion gradient between the two areas greatly increases.

Dr. Darrow has given us one explanation for how this occurs. According to his data, for every 3 moles of potassium lost from the cells only 2 moles of sodium are transferred from the extracellular fluid in exchange. This leaves a base deficit within the cells.

The data that have just been presented seem to indicate that perhaps the first mole of potassium to be lost is not replaced by sodium nor does any change in extracellular pH take place. As the next increments of potassium loss take place, there should be an equimolecular exchange with sodium. If this is true, then another explanation of the hydrogen-ion accumulation must be sought.

Some of the questions that have been raised today make us focus our thoughts upon what the state of intracellular anion is in such deficiency states. There must be labile anion fractions in the intracellular fluid which, under certain metabolic conditions, change their state so that they require more or less cation to maintain electroneutrality. Changes in hydrogen ion activity could be accounted for in this way. Dr. Guest has made a start in this direction.

DR. DANIEL C. DARROW, New Haven, Conn.: Dr. Cooke has given our position correctly. Dr. Miller and I first noticed that a loss of about 10% of muscle potassium could occur without

evidence of a disturbance in extracellular water and electrolytes. Beyond this minimum loss, further reduction in body potassium is not readily produced. The studies reported by Dr. Holliday substantiate this finding.

Dr. Cooke has stated that at present we have evidence that the initial small loss of muscle potassium serves as the first reserve mechanism in the defense against alkalosis. The transfer of extracellular Na to the cells in exchange for K reduces the elevation of serum bicarbonate which would otherwise occur with retention of Na or loss of Cl. Furthermore, renal conservation of body Cl is not as effective when body K is reduced as when abundant K is available. For this reason we may regard the loss of labile muscle potassium as removing the first line of defense against alkalosis from the body.

The loss of the readily available potassium from the body can occur in response to a number of stimuli. Dr. Miller and I observed this type of loss in response to large doses of potassium chloride. I would think it might be produced by sodium chloride, and we know it is produced by sodium bicarbonate. However, I am surprised that it can occur so rapidly on withdrawal of all electrolyte from food.

I have always believed that balances must predict body compositions that agree with the known variations found by tissue analyses. We know that excessive amounts of K do not occur in the body except when the serum concentration of K rises. We have been looking for high intracellular K for a number of years and have not found it, at least, in muscles.

I believe we must recognize two stages in K loss: (1) loss of labile potassium and (2) loss in excess of labile K. The first may not be of serious import, but the second indicates true potassium deficiency.

Balance techniques are fraught with many difficulties. I am sure I have encountered all the usual difficulties. In the past year, we have been determining the balances of normal infants with really extraordinary loads of sodium chloride and potassium. Over three days with the loads used we get no evidence from the balances that predict excessive losses or gains of body potassium in relation to N. The data are all compatible with preservation of relatively normal body composition, except that some of the retentions of Cl are a little too great—a least such retentions could not be maintained over long periods without producing unlikely changes in body composition.

We believe our success is dependent on including skin washings. While skin losses are not large, they are sufficient to correct the balances to ones that are compatible with normal body composition. I am reluctant to accept retentions such as were first shown. If after correction for skin losses, reasonable body composition is not predicted, other sources of error must be sought.

In our work I have interpreted balances in terms not strictly supported by the data. On the other hand, I have tried to indicate the assumptions and the order of magnitude of undetermined errors. We know that the balance technique gives insight on the changes in body composition which are not otherwise obtainable; the techniques are extraordinarily difficult and must always be interpreted in terms of the reasonableness of the changes in body composition which they predict.

Dr. Malcolm A. Holliday, Indianapolis: In comparing our data with the earlier data of Dr. Darrow, the figures I recall from the paper that Dr. Darrow expressed were 44 mM. per 100 gm. dry fat-free solids. Comparable figures for ours expressed in that manner were actually 40 mM. Ours is a more extreme situation.

The potassium lost in urine did amount to 4 mm. per kilogram of body weight, which is approximately enough to account for the initial reduction observed.

As to the anion that is lost with potassium, we have no data at hand. Obviously, it not only could be a loss of anion but a change in the equivalence of the anion, particularly phosphate, or in hydrogen ion, or some other unmeasured cation, as well. We merely wish to call attention to the observed loss of potassium. I think the striking thing in reference to that was the lack of any associated changes accompanying this loss.

As to the significance of the loss, obviously it would constitute a loss of the first line of defense, and we were not suggesting that people go on a potassium-free diet for that reason. But it does seem that we can lose a significant amount of potassium without what we classically

think of as potassium deficiency developing. I think this is a point we can agree on—that we can lose a significant quantity of potassium which does not necessitate a hurried repair—to apply this observation to clinical material.

The cow's-milk data referred to were described as a temporary gain. As we looked over the potassium retentions on cow's milk, we found it to be true that some of the data would indicate a greater retention of potassium than you could normally account for in body growth. I will confess that the findings in the particular study I selected here were a little higher than ordinary to demonstrate a phenomenon I was more interested in at this point, that is, the fluctuating nature, rather than the cumulative nature, of potassium retention.

I am not familiar, I am sorry to say, with Dr. Mudge's data, so I hesitate to put an interpretation on mine in reference to his, in answer to Dr. Gardner's remarks.

I don't know an appropriate period, in answer to Dr. Talbot's remarks, for adjusting to a new potassium intake. The paper which Dr. Gamble presented several years ago would seem to show that four days was not enough. Whether a longer period would be enough or not, I don't know. But four days is rather a long period in terms of balance studies, as those who have done them know.

The lower limit of potassium need on so-called periods of maintenance in patients who are not presumed to be deficient has been defined by Dr. Talbot, and I suppose the best way to define this need is that it represents the minimum turnover of potassium per kilogram of body weight; it must vary somewhere between 0.5 and 1 mEq. per kilogram. The animal can apparently tolerate 4 mM. per kilogram of body weight per day, and I assume on that intake he will select what he needs to repair a deficit.

I hesitate to take opposition to Dr. Wallace in his interpretation of the sequence of removal of 1 mM. of labile potassium and then 2 mM. of potassium to be exchanged for sodium in the case of alkalosis. It would appear from these data that you can lose the whole fraction of labile potassium and then start exchanging sodium for potassium on an equimolar basis.

The data has indicated to me that there are different mechanisms resulting in potassium deficits and the physiological significance of a deficit is determined by the physiochemical state of potassium left behind more than the absolute level.

In reference to the balance technique, it would be inappropriate to say that it did not have a place. I do wish we had done the studies on cow's milk in the more reasonable environment of New Haven; perhaps we would have gotten more reasonable data. But we have the data, and it has been presented as what can happen.

The Mechanism of Dysphagia in Bulbar-Pharyngeal Poliomyelitis. DR. JAMES F. BOSMA, Salt Lake City.

The observation of asymmetrical and deficient motion of the soft palate and walls of the oropharynx is of help in the diagnoses of bulbar-pharyngeal poliomyelitis, and the abnormalities seen are correlated with disability of the palatal sphincter as shown in "nasal" character of speech and in nasal regurgitation of swallowed fluids. There is a variable correlation of this disability of the upper pharynx with paralysis of the inferior contrictor muscles as evidenced by the accumulation of secretions in a hypopharyngeal pool.

The particular concern of this paper is with complete or near-complete prolonged failure of swallow in bulbar-pharyngeal poliomyelitis. In the past two poliomyelitis seasons, we have had an opportunity to observe on the isolation ward of the Salt Lake County General Hospital seven patients who have had a complete or near complete failure of swallow for a period of two weeks or longer. One of these patients had an essentially complete failure of swallow for a period of four months and two others for a period of two months. Our clinical observations of these patients have been supplemented by successive roentgenographic examinations employing a Fairchild camera which recorded serial exposures at half-second intervals. The superior surface of the palate and adjacent pharynx were visualized by iodized oil (Lipiodol) instilled into the nose, and the mouth and lower pharynx by iodized oil or thin barium. The patients were observed during efforts of swallow and during phonation in high pitch. A preliminary lateral film of a severely poliomyelitis-paralyzed pharynx showed the area of the palatapharyngeal isthmus to appear much expanded by reason of the abnormal pendant position of the palate. On the next example film taken during attempted but unsuccessful swallow there was little change in the internal contour of the pharynx. The combined mass of hyoid bone, base of

tongue, larynx, and attached lower portion of the pharynx rose but slightly. We are reminded that in the perspective of the stream of food the pharynx is a closed chamber having at its upper end a gate composed of adjoined palate and base of tongue and enclosed at the lower end by a sphincter formed of the lowermost fibers of the inferior constrictor muscle. In the initial motion of swallow the bolus gathered on the dorsal surface of the tongue is abruptly propelled through this gate into the pharynx coincident with an abrupt elevation of the entire mass of base of tongue, hyoid, and larynx. Though the intrinsic muscles of the pharynx, particularly in the area of the palate, do contribute normally to elevation of this hyoid mass, these muscles are apparently not essential for that motion. This is indicated very clearly by clinical observation of failure of swallow in coincidence with relatively little motor impairment in the area of the palate and, conversely, by successful elevation of the hyoid and its attached structures in subjects in whom there is marked paralysis of the entire intrinsic musculature of palate and pharynx. This is also indicated in our roentgenologic studies by inconsistency of demonstrated motion of the palate and the success of the general performance of swallow. It is equally apparent that the extrinsic muscles of the pharynx joining the tongue, hyoid, larynx, and pharynx to the base of the cranium and the mandible are essential to elevation of this "hyoid mass."

An additional problem which is found in some of these patients having polio-paralysis of the pharynx is that of an abnormal persistence of the sphincter at the junction of the pharynx and esophagus. This sphincter is indicated by the residual pool in the slide here projected and is also demonstrated by iodized oil instilled into the esophagus via a catheter while the patient is in Trendelenberg position, in which circumstance the iodized oil descends to outline the hypopharyngeal sphincter from its esophageal aspect.

Here, then, we have the disabled pharynx, unable to initiate the motion of swallow, to fill itself, and, also, it may be unable to empty itself of the secretions which accumulate within it from the adjacent mouth, nose, and respiratory tract. The significance of this failure of the initial stage of swallow may perhaps be inferred from current electromyographic studies of the event of swallow currently in progress in collaboration with Dr. Robert Doty, of the department of physiology of our school. In this multiple-channel electromyograph, we note that the swallow as it is induced reflexly is represented by activity appearing successively in the superior, middle, and inferior constrictor muscles. This is a consistent sequence in the event of swallow and apparently is not subject to modification when once initiated. Thus, in the circumstance of clinical poliomyelitis, it is perhaps particularly meaningful that we so commonly lose the first stage of this consistent sequence as a result of paralysis of the muscles elevating the structure centered about the hyoid bone. And, thus, we lose not only this initial function but we seem to lose the entire coordination sequence of swallow.

An additional observation of these patients which is of interest neurologically is that in the circumstance of absence of swallow they demonstrate an exaggeration of the gag reflex, which reflex progresses readily to retching. It is also noted that the area of elicitation of this exaggerated gag reflex is also increased to include the inferior aspect of the soft palate and the dorsal surface of the posterior half of the tongue. Turning again to the electromyographic studies, we have noted that the two major coordinations of gag and of swallow are clearly distinguished and also are strictly alternative. Thus, when the one coordination pattern is invoked, the opposite coordination pattern of swallow is apparently inhibited. It is possible that this exaggeration of the gag reflex may be a mechanism contributing to the persisting disability of swallow in these patients.

DISCUSSION

Dr. Frederic N. Silverman, Cincinnati: We have had the opportunity to examine by fluoroscopy a few children with pharyngeal paralysis in bulbar poliomyelitis. The disturbance of swallowing observed stands in sharp contrast with the act of swallowing noted in healthy children. Dilatation of the pharynx and hypopharynx during the act of swallowing in children with paralysis is generally much more marked than revealed in Dr. Bosma's slides; this is so, probably, because Dr. Bosma has limited his illustrations to certain phases in the total swallowing act.

The normal mechanism of swallowing has been shown very beautifully in cinemaroentgenograms by a group in Rochester. The motion pictures show clearly how the act of swallowing

is initiated by the dorsum of the tongue which throws the opaque bolus back into the pharynx. This action is demonstrated in Dr. Bosma's slides, which also indicate that the subsequent action of the pharyngeal muscles is deficient in his patients.

I should like to add a note of caution about the use of iodized oil in roentgen studies of the swallowing mechanism. Iodized oil has a tendency to spread over the surface of the mouth and pharynx and even into the larynx in infants in whom aspiration of this type is never found when a barium suspension is used. In young infants in whom we have no reason to suspect any aspiration phenomena the use of iodized oil will very frequently result in an erroneous impression of disturbed swallowing mechanism.

We have observed one patient with pharyngeal paralysis whose success in overcoming her difficulty supports Dr. Bosma in likening the action of normal pharyngeal muscles to that of a pump. The patient was a 15-year-old girl who was unable to swallow and had been fed for some time by stomach tube. We thought there was a large element of hysteria in the persistence of the difficulty. She finally discovered her own way out of the situation. She would throw a bolus of food into the paralyzed pharynx by normal tongue action, and then, holding her nose with her fingers, attempt a forced expiration. In this way, a Valsalva effect was produced, and the bolus was pumped into the esophagus. With fluoroscopic control, we could see the pharynx dilate, and then the bolus would be pushed past the constricting action of the pharyngoesophageal junction.

Melena Neonatorium: The Swallowed-Blood Syndrome. Dr. Leonard Apt and Dr. William S. Downey Jr., Boston.

One of the causes of melena neonatorum has been said to be the ingestion of maternal blood during the labor period. The present study was undertaken in order to ascertain whether blood introduced into the stomach of a newly born infant can cause grossly bloody stools and to describe a method by which bloody stools caused by the ingestion of maternal blood can be differentiated from similar stools caused by hemorrhage in the baby's digestive tract.

Measured amounts of blood taken from adults or the cords of newly born infants were given by gavage to babies within several hours after birth. A relatively large amount of blood (35 to 40 ml.) was necessary to produce melena in the majority of babies. A second group of older newly born infants whose meconium had been evacuated was also studied. In contrast to the first group this second group required much less blood (10 ml.) to produce grossly bloody stools.

A simple test was devised to enable one to differentiate maternal from baby's blood in a grossly bloody stool. The test was based on the fact that maternal (adult type) hemoglobin is changed from an oxyhemoglobin solution (pink) to an alkaline hematin compound (yellow) in one to two minutes after the addition of alkali. The hemoglobin of a newly born infant, however, is predominantly of the fetal type and is alkali resistant. The pink oxyhemoglobin solution therefore persists in this interval. A stool must be grossly bloody and not tarry in order to observe this change. The validity of the test was confirmed by the successful differentiation of cord blood (predominantly fetal hemoglobin) and blood from adults, given by gavage, in the grossly bloody stools.

With the use of this test we were able to predict the benign course of five patients with melena admitted to the hospital or seen in the newborn nursery.

A review of the obstetrical history revealed that all the mothers had had a premature separation of the placenta with vaginal bleeding prior to delivery. In four of the five mothers bloody amnotic fluid was noted. It is suggested that maternal blood may enter the amniotic fluid thru a tear in the membrane associated with separation of the placenta.

Dr. Irving Schulman, New York: I should like to add a few comments. First, I think it should be pointed out that a fair number of infants, newborn infants, have as little as 50% hemoglobin—54, as a matter of fact, was our lowest figure—so that I can visualize certain instances where this test, although it seems to be helpful, may get one into a little difficulty wondering whether it is fetal or maternal blood.

On the chart just prior to the last one where the four infants were noted, I noticed one baby had a hemoglobin value of 11.8, one of 12.5, and the third of 13, all of which are unusually low values for hemoglobin in a baby 1 or 2 days of age. I should like to ask for an explanation of this.

DR. EDWARD C. CURNEN JR., Chapel Hill, N. C.: The technique which Dr. Apt has described is certainly simpler than identification of blood in the stools by serologic methods. I should like to ask Dr. Apt if he has made observations on how long blood can be detected in the stools of infants following a single experimental feeding.

DR. RICHARD L. DAY, New York: I hope others are as chagrined as I am at myself for not having thought of this very useful test. We struggled with the identification of the blood being passed by a premature infant as late as 72 hours after delivery and did succeed by typing the cells in showing that it was mother's blood. In another instance, blood typing failed to identify the blood with certainty. Dr. Apt's method seems to be more accurate and much simpler.

DR. LEONARD APT, Boston: Dr. Schulman has raised two pertinent points. Although occasionally as much as 40% of a newborn baby's hemoglobin may be of the adult type, the interpretation of the qualitative test which distinguishes adult from fetal hemoglobin in the bloody stool has not been difficult. Two minutes after the addition of alkali to the hemoglobin solution made from a bloody stool containing a newborn baby's blood, a distinct pink has persisted in spite of the slight color change than may result from denaturation of the adult type hemoglobin. If the hemoglobin had been of maternal origin (adult type) there would be no pink color after the addition of alkali. The control test using the infants' peripheral blood has been a useful guide as to extent of color change that one may expect after addition of alkali.

An explanation for the slightly low hemoglobin concentrations encountered in several babies in the group that were thought to have swallowed maternal blood is not simple. Perhaps in the premature separation of the placenta the tear extended to the fetal side of the circulation. Another factor that may account in part for the infants' lowered hemoglobin concentrations was the early ligation of the umbilical cord in dealing with the complicated labor. There was no appreciable decrease in the hemoglobin concentration during the hospital stay as one would expect if the bloody stools were due to intrinsic hemorrhage.

The question in regard to the duration of blood in the stools after it was given by gavage can be answered by observing the data on the next slide. The amount of blood given (5 ml. increments) is correlated with the time of appearance of the first bloody stool, the duration of the bloody stools, and the number of bloody stools passed during this period. Similar values are given for the presence of occult blood. The duration of bloody stools after the intragastric administration of blood was as follows: 40 ml., 14 to 28 hours; 30 ml., 12 to 45 hours, and 20 ml., 32 to 40 hours.

I wish to thank Dr. Day for his comments. We attempted to determine the blood group of the blood in stools as another method of distinguishing between maternal and infant's blood. The technique was a modification of the one used by the Department of Legal Medicine to determine the blood group in a blood stain. The method was abandoned because of the following disadvantages: (*a*) it required the preparation of antisera of a certain range of potency; (*b*) the technique involved many steps and one had to use control tests with saline and human A and B erythrocytes; (*c*) the test took over two hours to complete because of two one-hour incubation periods; (*d*) the mother and infant's blood may be the same type; (*e*) the presence of blood group activity of meconium in "secretors" may interfere with accurate blood-group identification and differentiation.

The alkali denaturation test requires only water and sodium hydroxide, and is performed in less than five minutes.

Serum Complement Levels in the Nephrotic Syndrome. DR. RUTH ALICE DAVIS and DR. CONRAD M. RILEY, New York.

Serum-complement levels were investigated in children with the nephrotic syndrome, in relation to corticotropin (ACTH) and cortisone therapy. Ten patients were given cortisone orally, 200 mg. per day for 7 to 11 days, and one received corticotropin intravenously, 10 mg. per day for 10 days. With the exception of one patient in the cortisone group, all responded with a marked diuresis. These patients could be divided into two groups on the basis of duration of the disease before treatment. Five had been sick for only one month or less, and six had had the disease for a period varying from four months to two and one-half years. The behaviour of the serum complement was different in the two groups. The initial complement level before therapy was, on the whole, higher in the patients of the former group than in

those of the latter group. In three of the new cases, the titer was actually normal. During therapy, the course of complement was inconsistent in the cases of less than a month's duration. In contrast, in all of the cases of longer duration, complement stayed at or fell to significantly low levels at some time during therapy. The only consistent change in both groups was a rise of complement to normal or elevated levels with diuresis. In the one case in which there was no diuresis, complement never reached normal.

Beginning one week after cessation of the long course of hormone therapy, seven patients were then given repeated three-day courses of cortisone administered orally, 200 mg. per day, at approximately weekly intervals. After the first six courses, the interval was prolonged to two to four weeks. The total number of courses received varied from 4 to 11. Complement remained high or normal in all but one patient as long as the courses were continued at weekly intervals. Thereafter, it continued normal for varying intervals up to three and one-half months. The individual short courses did not produce any consistent change in complement level. Three patients remained edema-free for a total of two to three and one-half months after diuresis, relapsing then with upper respiratory infections. Three others have remained edema-free to the present, for periods of one and one-half, five, and five and one-half months, despite upper respiratory infections. Two of these have shown improvement in their laboratory findings. The course of the seventh patient indicates that relapse is possible on this regimen. After only three courses, he had a relapse associated with an upper respiratory infection and a fall of complement level significantly below normal.

A gross inverse relation between serum-complement level and degree of edema has been demonstrated. Corticotropin and cortisone probably have only an indirect effect on complement through mechanisms not understood. Because of the inconsistency of the findings in the early cases, changes in complement titer probably can not be explained as simply as to assume that they are only reflections of an antigen-antibody combination. The possibility of additional explanatory factors makes further investigation necessary.

DISCUSSION

Dr. Walter Heymann, Cleveland: I think that Dr. Davis and Dr. Riley should be congratulated for the studies, especially as they have carried them out in details followed in one and the same child. The interpretation of the results is intriguing. The antibody-antigen reaction, if involved in this disease, may lead to a compliment drop. That has been shown in the experimental disease of the rat, where after the injection of a nephrotoxic serum the complement drops precipitously, but, in contradistinction to the disease of the child, rises within an hour after, to stay normal despite continued disease.

I should like to have Dr. Davis's and Dr. Riley's opinions on whether they do or do not believe that another factor may be at play. I want to refer to an excellent piece of work done six or seven years ago by Ecker and Seifter, who, in four of our nephrotic children in Cleveland, studied the excretion of complement in the urine. They found that complement is not lost in the urine en bloc, but they followed the excretion of complement in its different components and found that *C'2* was readily and *C'3* and *C'4* quite well excreted; *C'1* was not at all in the urine.

The determination of complement fractions in the urine is exceedingly difficult. It would be a great deal of work to follow this in children at the same time that the serum complement is studied. One could possibly get an approach easier by studying the excretion of albumin and globulin in the urine of these children, as complement is part of the globulin fraction. If we recall that as much as 50% of the proteins in the urine of nephrotic children may be globulins, the probability is good that complement may be lost in the urine and thus account for the serum depletion.

Dr. Frederic Moll, Seattle: I think it is rather difficult to draw comparisons between the experimental work in the animal and the patients we have seen here today. However, I should like to ask, in view of the fact that in my studies with experimental animals we have found a regular drop in complement in the normal animal just upon administration of cortisone, depending upon the dose, and this seemed to be borne out to some degree here, whether the drop in complement is related to the dose and size of the child.

The other question I should like to ask is whether because in the determination of complement lipemia interferes, the rise in complement could be associated in any way in these patients with the change in the serum lipemia as well as of edema.

DR. ROBERT KELIN, Pittsburgh: I should like to ask a very obvious and simple question. Were there any measurements of albumin—that is, along with the measurements of serum complement—as an index of the amount of overhydration and volume changes?

DR. RUTH ALICE DAVIS, New York: Thank you very much for your comments.

Certainly more detailed investigation of the excretion of complement in the urine of patients with the nephrotic syndrome is warrented. The possibility that, accompanying therapy and diuresis, there are changes in urinary output of complement or of one of its four fractions should be studied.

It is of interest that Lange has reported that he was unable to find complement in the urine of patients with the nephrotic syndrome, in contrast to the previously mentioned findings of Seifter and Ecker.

The magnitude of the drop in complement level with cortisone therapy and of the subsequent rise with diuresis does not appear to be related to the size of the child or the dose of cortisone. The same cortisone dose was used in all these children. The sizes of the patients varied markedly. The ages ranged from 16 months to 7½ years. Comparable changes in complement level were seen in children of different sizes.

The question of association between changes in complement and changes in degree of lipemia has not been studied. We have, however, noted no consistent alteration in gross serum turbidity associated with variations in complement titer.

Also, we failed to show any correlation between urinary protein output (measured qualitatively) and the complement level.

The Role of Diphtheria-Tetanus-Pertussis Vaccine as an Inflammatory and Localizing Agent. DR. JOSEPH ZIEGLER, Philadelphia, and DR. MORTON KLEIN, Perth Amboy, N. J.

Alum-precipitated diphtheria-tetanus-pertussis vaccine may cause localization of paralysis in a small percentage of persons when given during the poliomyelitis season. The intramuscular injection of gelatin, however, did not cause any localization of paralysis when used as a control injectant during the recent extensive trials of gamma globulin. In an attempt to explain this difference in the localizing effect of the two agents, studies were carried out in white Swiss mice. It was found that diphtheria-tetanus-pertussis injected intramuscularly into the hind legs of mice caused a prolonged inflammatory reaction as determined by section of the leg where the inoculation was done. In further experiments, gelatin was inoculated into one leg of the mouse and diphtheria-tetanus-pertussis vaccine into the opposite leg. At various intervals 1% trypan blue was injected intraperitoneally. The dye localized in the leg inoculated with the diphtheria-tetanus-pertussis, but not in the leg inoculated with the gelatin. Other agents, such as aqueous penicillin and purified diphtheria toxoid, failed to cause any localization of the dye. Since it is now believed that viremia may precede the onset of paralytic poliomyelitis, our results suggest that diphtheria-tetanus-pertussis vaccine induces a prolonged inflammatory reaction which creates a suitable site for the localization of virus present in the blood stream; the subsequent paralysis may be referable to the leg where the inoculation was done.

DISCUSSION

DR. HAROLD FABER, San Francisco: As I will bring out in another paper, the theory that localization after immunization is referable to already established infection does not fit in with the interval between injection and the onset of symptoms of paralysis in humans, save in quite rare instances. The interval is usually the normal incubation period of poliomyelitis. This suggests that the reason for paralysis after injection is probably related to simultaneous, or almost simultaneous, introduction of the immunizing agent and of the virus itself.

However, the question as to whether certain substances can promote this localizing reaction remains open. I cite a series of experiments by Miss Silverberg, Mr. Dong, and myself, performed three years ago on monkeys, in which virus was mixed with a variety of substances and inoculated into a single limb. The mixture of diphtheria and tetanus toxoid with pertussis vaccine in aluminum hydroxide, known as Alhydrox, gave the largest proportion, and a very high proportion, of localized paralysis. The mixture of virus and pertussis vaccine alone produced localized paralysis in a smaller percentage of cases. Virus and penicillin procaine did not produce localized paralysis, with a single exception. A mixture of virus and aluminum hydroxide alone did not produce it, nor did a mixture of virus and saline.

I am inclined to believe then that either diphtheria toxoid, tetanus toxoid, or, possibly, pertussis vaccine alone, may promote localization.

Dr. Bela Schick, New York: There are three observations which show the influence of the inflammatory process on the localization of virus. One I published myself. It was the flaring up of a positive tuberculin reaction during the measles process. Usually, the measles process supresses the tuberculin reaction. I was very much astonished when I saw a flaring up of a previously positive and already fading tuberculin reaction. The explanation was that the measles localized early in the area of the previous positive tuberculin reaction.

The third observation is known in the Orient. The women selected for the harem came from Tscherkassia. The women, when inoculated with smallpox, rubbed their legs with irritating substances during the incubation time in order to draw the virus to the legs so that the face would be as much as possible free from pustules of smallpox.

Dr. A. Ashley Weech, Cincinnati: I think this is a beautiful piece of work, but in a highly inflammable period when the country is aroused about how to distribute its insufficient supply of gamma globulin it is well, I think, to reflect soberly before drawing any conclusions from it that may affect our program.

Recently, Dr. Sabin and I, and that means chiefly Dr. Sabin, have had an occasion to analyze in our own way the data presented by Hammond in respect to the effect of gamma globulin, in the three areas in which it was tried last summer.

On the basis of number of cases and type of results obtained, one is forced to say that no conclusion whatever can be drawn from the data obtained in Texas and the data obtained in Utah. Only the data in Iowa seemed to indicate that there has been a marked effect of gamma globulin, or significant effect, I should say, in suppressing the incidence of paralytic poliomyelitis.

Now, if one takes Hammond's last data, which he was asked to provide concerning the incidence of poliomyelitis in the community at large in the group of children—that is, who were not inoculated with either gamma globulin or gelatin—and divide the figure into three periods, as Hammond does, 1 to 2 weeks after closing of the clinics, 2 to 4 weeks after closing of the clinics, and 4 to 14 weeks after closing of the clinics, one will observe in the first group no difference between the incidence of paralysis in the noninoculated group and in the group given gamma globulin but a much enhanced incidence in the group which received gelatin.

Hammond himself discredits this fact by saying that the more intelligent families who attended the clinics would have had better reporting of the incidence of poliomyelitis and thus explains the facts. However, if this were true, one would expect the same difference in the 2- to 4-week group and in the 4- to 14-week group. In this group, one finds the reverse is true, that the incidence in the gelatin group is lower than the incidence in the noninoculated group. If, then, one wipes out the entire effect of comparing gamma globulin groups with gelatin groups, one finds that gamma globulin in Iowa seems to have exerted a beneficial effect, not from just the 2nd to the 4th or 5th week but from the 2nd to as long as the 14th week, and, on examining the figures, one is led to ask why there should be such a striking difference between what happened in Iowa and what happened in Texas, and, on the other hand, could the entire differences be explained by a transient two-week period of acceleration of the tendency to paralysis in the group receiving gelatin? One more point: everyone is looking for an effect of localization of the gelatin as regards the site of paralysis in the affected cases. The incidence of poliomyelitis in both groups was high enough that if gelatin only had a slight enhancing effect that effect would have accounted for the difference but the number of cases would have been lost in the grand total.

Dr. Lewis Coriell, Philadelphia: I should like to discuss a little bit the interpretation given by Dr. Weech and attributed to Dr. Sabin. We have analyzed our material very carefully and in great detail and have submitted the data to several disinterested statisticians and epidemiologists. The published conclusions represent the concensus of these analyses. Dr. Sabin's interpretation is at variance with these combined opinions. I am not quite sure just how he has analyzed the data without seeing figures and tables. I gather, from what Dr. Weech said, that he has taken some of the data out of context and made a statistical comparison without taking into account the many epidemiological factors which are involved.

In planning the gamma globulin field trials it was postulated that those more intimately exposed to known cases would volunteer for injections best, and, therefore, expected disease

rates would be higher among volunteers than among noninjected children. For this reason, it was deemed necessary to give half the volunteers injections of gelatin to serve as controls on the children injected with gamma globulin. The results show few cases among the children who received gamma globulin, a higher rate among those not given injections, and a still higher rate among the gelatin controls. The figures alone might suggest that gelatin precipitated paralysis, but all the supporting evidence from epidemiological, clinical, and statistical analyses suggest that this was not the case. We could find no supporting evidence that gelatin precipitated paralysis. This is presented in detail in the published reports.

I think this study of Dr. Ziegler and Dr. Klein is extremely interesting. It corroborates previous information that inflammation does cause localization of particulate matter. It is just one more reason for questioning our immunizing processes, and perhaps we should use more fluid toxoids instead of alum-precipitated antigens. It is interesting that gelatin did not cause an inflammatory reaction or localization of dye.

DR. JOSEPH ZIEGLER, Philadelphia: If we limit this discussion to the questions related to the present work, we will not be too long. I am not going to discuss the relative merits of gelatin as an innocuous agent or gamma globulin as a prophylactic agent. We elected to use gelatin after Hammond and co-workers reported that the intramuscular injection of this material during an epidemic did not increase the incidence of paralytic poliomyelitis. When we injected gelatin into the animals, we could demonstrate neither the gross localization of dye nor histological evidence of inflammation. The original report of Bradford and Hill and the reports of other investigators which have followed indicate that when the injectants were known the alum-precipitated vaccines were associated with the paralytic form of the disease with a high degree of statistical confidence.

In our studies, we found both the gross localization of dye and inflammatory reaction at the same site followed the injection of the alum-precipitated vaccines. We did not study gamma globulin at this time.

In answer to Dr. Faber, we are in complete agreement with the fact that the time at which one elects to inject the material intramuscularly is critical. In the original study by Bradford and Hill, their statistical analysis revealed that the correlation of the double event, the intramuscular injection and the onset of paralytic poliomyelitis, was clearly demonstrated when the interval was 30 days or less. In our investigation, we demonstrated that the gross localization of the dye and the inflammatory reaction were present for 30 days following the intramuscular injection of the alum-precipitated pertussis, diphtheria, and tetanus mixture. This is suggestive that the inflammatory site may be fundamental to the phenomenon of paralytic poliomyelitis which follows the injection of certain materials.

In answer to Dr. Schick, who has also demonstrated that certain viruses may become localized at the inflammatory site, we are still faced with the problem of finding the virus of poliomyelitis at the inflammatory site. This aspect of the problem is under investigation.

In answer to Dr. Weech and Dr. Coriell, I am certain that I am not qualified to discuss the relative merits of gamma globulin and gelatin. I leave this to be clarified by the epidemiologist and statistician.

Propagation in Tissue Cultures of Cytopathogenic Agents Apparently Derived from Varicella Vesicle Fluids. DR. THOMAS H. WELLER and HELEN M. WITTON, M.S., Boston.

In a previous report (Weller and Stoddard: *J. Immunol.* **68**:311-319, 1952) we described the development of intranuclear inclusion bodies following the inoculation of suspended cell cultures of human tissues with varicella vesicle fluid. Efforts to maintain the responsible agent on serial passage in suspended cell cultures were unsuccessful. More recently, roller-tube-cultures of various human tissues have been applied to the same objective. Following the inoculation of roller cultures with vesicle fluid materials from cases of varicella, six agents have been isolated which produce focal cytopathogenic lesions of a characteristic nature. The focal lesions first become apparent on the sixth to eighth day after inoculation, presenting as collections of swollen rounded hyaline cells. In the center of the focal areas the cells gradually degenerate, while at the periphery of the focus slow extension of the process occurs, seemingly as the result of progressive involvement of cells in physical contact with the affected area. Study of stained preparations has revealed that the changes in cellular morphology observed in inoculated

cultures are characteristically associated with the presence of intranuclear inclusion bodies. Occasionally the larger swollen cells are multinucleate, with each nucleus containing an inclusion; these cells resemble the giant cells described by others in the cutaneous lesions of man. All six of the agents have been propagated serially in tissue culture, as evidenced by the continuing development in subcultures of focal areas of cellular enlargement and degeneration. Employing tissue suspensions as the passage material, two of the agents have now been maintained for 10 passages or a cumulate period in cultivation of 124 days. A peculiarity of these agents in culture has been the apparent failure of infectious material to appear in detectable amounts in the fluid medium. Tissue suspensions infective for cultures have been without obvious effect when inoculated into suckling mice or into the developing hen's egg by various routes. These findings indicate that we are not dealing with the virus of herpes simplex.

Following the inoculation of roller-tube cultures of human tissues with fluids obtained from the eruptive lesions of two cases of herpes zoster, two cytopathogenic agents have been isolated. These agents also produce focal lesions composed of rounded swollen cells which characteristically contain eosinophilic intranuclear inclusion bodies. Employing inoculum consisting of ground tissue suspensions, these agents have been maintained in serial passage; one has been carried through four passages for a cumulate period in cultivation of 66 days. Neither of these agents is overtly pathogenic for newborn mice.

No evidence is now at hand which would suggest that the agents so isolated in roller-tube cultures are not in fact the causative agents of varicella and herpes zoster. Studies designed to elucidate their nature and to investigate the interesting question of their possible coidentity are in progress.

DISCUSSION

DR. LEWIS CORIELL, Philadelphia: I should like to congratulate Dr. Weller on this fine achievement and point out that he is one of many who have been trying for years to propagate this virus in the laboratory. Dr. Goodpasture did have a single passage in 1933, as have others since, but Dr. Weller is the first to pass chicken-pox virus serially in tissue culture.

I should like to point out also that Dr. Weller has just gone back to this work recently, after an interval of several years devoted to the cultivation of poliomyelitis viruses in tissue culture. You will recall that he was trying to cultivate the viruses of herpes zoster and chicken pox, originally, when one day some poliomyelitis virus was placed in a few extra tissue-culture tubes. The poliomyelitis virus grew, and this knowledge revolutionized laboratory research in poliomyelitis and promises to lead to an effective vaccine in the near future. Two such advances from one laboratory in the course of four years is high tribute to the work of Dr. Weller and his colleagues in Boston.

I should like to ask Dr. Weller what fixative and staining technique he used. Most of the inclusion bodies that he showed were shrunken, with a halo of clear material between the inclusion body and the rim of the nucleus, which, as Dr. McNair Scott has pointed out in herpes simplex, is the indication of an old inclusion body. Perhaps these inclusion bodies were shrunken away by the fixatives. Did they fill the whole nucleus when you looked at them directly without staining?

Evidence that the inclusions shown here are not herpes simplex might be adduced from a small detail in the photomicrographs. That is, when the inclusion body of herpes simplex starts to form, the nucleolus disappears, whereas in the pictures shown by Dr. Weller the nucleolus was very prominent.

The necessity for transferring whole infected cells to obtain serial passage may explain the frequent failures in the past; however, it seems probable that improved cultures and nutrient media will eventually permit the survival of virus outside the intact cells.

DR. MORTON KLEIN, Philadelphia: You mentioned that you didn't get any neutralization. I guess you did mix the virus and convalescence serum prior to inoculation into the tissue culture. That is, of course, unique for virus infections. Would you care to comment, if you can, further about that?

DR. T. H. WELLER, Boston: I greatly appreciate Dr. Coriell's remarks. It would seem likely that the characteristic focal distribution of the numerous inclusions observed in our preparations will provide nice material to work out the morphological aspects of the so-called life cycle of the inclusion bodies. The reference to the use of tissue suspensions for the passage of the agents

and the second question with regard to the neutralization technique employed are really part and parcel of the same problem. I think it is important to stress that apparently we are dealing with an agent or agents that behave differently from anything we have worked with in the laboratory before. For example, vaccinia virus, the poliomyelitis viruses, the Coxsackie viruses, and mumps virus all may be found in the fluid phase when they are propagated in tissue cultures. However, with the agents described today, we have been unable to carry out tissue-culture passages using cell-free fluids. We can pass them only when the inoculum consists of ground tissue. Whether that means that there are live cells in the inoculum, or else that the agents are in some manner attached to the tissue fragments—there are also other possibilities—we don't know. Thus far, neutralization tests employing paired sera from cases of varicella have been negative. It is possible that the negative results merely reflect the apparent close affinity between the agents and the tissue components of the cultures.

Studies on the Metabolism of Fibrinogen in Congenital Afibrinogenemia. Dr. David Gitlin and Dr. Wayne H. Borges, Boston.

Afibrinogenemia, a hemorrhagic diathesis associated with a clotting time of infinity, is presumably due to the absence of circulating fibrinogen. Since this deficiency may result from errors either in synthesis or degradation, two children with congenital afibrinogenemia were studied to determine the nature of the metabolic defect and to obtain information concerning the presence of an extravascular fibrinogen pool. Immunochemical methods were employed in this study to estimate fibrinogen specifically and independently of other factors involved in the clotting mechanism.

The rate of disappearance from the plasma of intravenously administered fibrinogen has been studied. More than half of the administered fibrinogen disappeared from the circulation in the first 48 hours, emphasizing that, at equilibrium, the mass of fibrinogen present extravascularly is approximately equal to the mass of fibrinogen within the blood vessels. After the first two days, the fibrinogen followed a logarithmic decay curve with a half-life of about four days, a value approximating the half-life in the normal person and indicating that the fundamental defect in these patients is a failure to synthesize adequate quantities of fibrinogen. The failure in synthesis is not complete, however, and traces of fibrinogen, about 1 mg. per 100 cc., were detected in the plasma of each patient prior to infusion of fibrinogen.

Fibrinogen in the tissues of the normal child, as detected by fluorescein-labelled antisera, is found chiefly in the connective tissues and vascular and lymphatic channels. In congenital afibrinogenemia, the connective tissues in biopsies of skin and muscle were found to be specifically deficient in fibrinogen; this deficit could be quickly rectified by the intravenous administration of fibrinogen.

An Epidemic of Acute Glomerulonephritis in Children Associated with a Specific Serological Type of Group A Streptococcus. Dr. Alan C. Siegel, Dr. Harold I. Griffeath, Dr. William Langewisch, and Dr. Arthur C. Maimon, Warren Air Force Base, Wyo.

An outbreak of acute glomerulonephritis in an elementary school in Wyoming serves to reemphasize the importance of Group A Type 12 streptococci in the production of acute nephritis.

Attention was called to this epidemic by two clinical cases of acute nephritis occurring in siblings, one of whom attended kindergarten. A cultural survey over a 10-week period revealed an epidemic of streptococcal disease involving 71% of 185 children attending the kindergarten and a second grade occupying the same floor in the school building. Forty percent of the children with positive throat cultures were found to harbor Type 12. Urine samples were obtained weekly over the same period from 72 children harboring Group A streptococci.

Two patients with clinical signs of acute nephritis and two children with gross hematuria were encountered. Twenty-seven of the 72 children (38%) were found to have microscopic hematuria. Two-thirds of these children with hematuria were found to harbor Type 12 streptococci. Two additional cases of acute nephritis occurred, one in the preschool sibling previously described and the second in a 2-year-old child who lived between two kindergarten students carrying Type 12 streptococci. The four patients with clinical signs of nephritis were associated with Type 12 streptococcal infections.

These data indicated that this strain of Type 12 was markedly nephritogenic. The recognition of the onset of an epidemic due to a nephritogenic strain should make it possible to institute control measures to prevent further cases of nephritis.

DISCUSSION

DR. HENRY L. BARNETT, New York: I should like to ask a little more about the technique of collecting the urine specimen. I am well aware of the difficulty of obtaining timed specimens in children of this age, and without meaning to cast doubt on the validity of the relationship between these Type-12 infections and the occurrence of acute nephritis, I should like to emphasize the necessity for proper examination of the urine in the diagnosis of acute nephritis.

I should like to know how soon the urine was examined after it was collected and if any attempt was made to get timed specimens.

DR. LEWIS CORIELL, Philadelphia: This raises several questions which we have to think about, and I should like to have Dr. Siegel's comment on the interpretation of these data in connection with penicillin therapy of streptococcal infections in the home, where typing of streptococci is not practical with present techniques. What is the possibility of immunizing infants and children against Type 12, for instance, or, perhaps, of immunizing with selected type-specific streptococci those children who have already had one attack of rheumatic fever or nephritis?

DR. DANIEL C. DARROW, New Haven, Conn.: I was tremendously interested when Dr. Rammelkamp reported that acute nephritis is associated with specific types of streptococci. I knew that Dr. Trask and Dr. Boisvert had typed all the streptococci in New Haven from 1938 until some time during the war. My interest in acute nephritis was intensified by the decrease in incidence of acute nephritis which occurred gradually following the introduction of sulfonamides. The incidence in our clinic decreased from about seven a year to almost none by 1945. In the past two or three years, the incidence of acute nephritis seems to be returning to the former level.

A review of these records supports the findings of Dr. Rammelkamp of high incidence of Type 12 streptococci in nephritis. In keeping with their findings, we also found a few cases associated with Type 4. However, I was surprised to find almost as many cases with Type 14 as Type 12. Inquiry indicates that the typing is difficult but unlikely to be erroneous. I understand that Dr. Rammelkamp has observed over 1,000 cases of Type-14 infections, without 1 case of acute nephritis. I wonder if Dr. Rammelkamp has any ideas which will reconcile his findings with those of New Haven.

DR. CHARLES RAMMELKAMP, Cleveland: I think the evidence that certain types of streptococci produce acute nephritis much more readily than others is now well established. We know of 10 or 12 epidemics where Type 12 has been isolated, and, in addition, we have some evidence at the present time of one Type-4 epidemic.

If we go into the past, it is very difficult to relate nephritis to specific types when the typing was done by the Griffith agglutination technique. Anyone that has had much experience with this technique knows that it is exceedingly difficult. The organisms typed a number of years ago with the Griffith method, when retyped today with the M-protein technique, frequently do not confirm.

On the other hand, knowing the workers at Yale, I would suspect that the Type 14 at that time may well have been nephritogenic. If we look through the literature, we find that, indeed, certain other types probably have produced some nephritis in the past. For example, Type 31 in Denmark was isolated from 20 patients with scarlet fever and in 6 acute nephritis developed.

I would suspect that any type may, at times, cause nephritis, but the primary types responsible for nephritis change over the years. In this regard, it is interesting that we can go now into the past history of nephritic patients and show by special serological techniques that persons with acute nephritis have been infected with these nephritogenic strains. One can demonstrate antibody to Type-12 streptococci for at least six years after the patient recovers.

DR. ALAN C. SIEGEL, Warran Air Force Base, Wyo.: Thank you, Dr. Barnett, for giving me an opportunity to mention our technique. The 10-minute period did not allow that.

Briefly, we use a modification, if I may use the expression, of the Addis technique. All urine samples that we collected were examined within two hours after passage, and the urine is

placed in a graduated centrifuge tube. Ten cubic centimeters of urine are spun at 1,500 rpm for 15 minutes in an International Centrifuge No. 2. The supernatants are then poured off, and the sediment is collected, to be resuspended in 0.5 cc. of fluid.

This sediment is then twentyfold concentrated and examined in a hemacytometer chamber. When we count 200 or more red cells in 0.9 cu. mm., counting all nine squares of the chamber, we consider that to be hematuria, and since it is twentyfold concentrated urine divided by 20, it gives us 10 red cells per cubic millimeter. To relate that to the Addis count, that represents 10,000 red cells per cubic centimeter of unconcentrated urine, and if a 6- or 7-year-old child puts out between 500 and 700 cc. of urine in 24 hours, this would amount to between 5,000,000 and 7,000,000 red cells in 24 hours, which would be well outside the limits of normal.

In answer to Dr. Coriell's question, we feel that streptococci can best be eradicated by parenteral administration of penicillin, as evidenced by papers coming out of our laboratory. In order to completely eradicate and get maximum antibody suppression, penicillin should be given so as to cover the patient for 10 days.

We have used orally administered penicillin, 1,000,000 units twice a day, for prophylaxis over a 10-day period and have obtained adequate protection.

As far as vaccine goes, at the present time we have not been able, from the people who are doing work in that field, to secure an adequate vaccine which gives good antigenicity and good antibody response without side reactions.

Experimentally Produced Pulmonary Vascular Changes: Their Relationship to Similar Changes Found in Congenital and Acquired Heart Disease. Dr. J. Francis Dammann Jr. and Dr. William H. Muller Jr., Santa Monica, Calif.

The pulmonary vascular changes that are present with certain forms of congenital and acquired heart disease have important prognostic significance. We have successfully produced similar changes in experimental dogs in which the distal left pulmonary artery was severed from the main pulmonary artery and anastomosed to the side of the aorta. Thus the circulation to the left lung was entirely from the aorta and that to the right lung from the right ventricle. The clinical course in the five dogs which survived this procedure beyond one week varied directly with the size of the anastomosis. Dogs with a large anastomosis were less active, gained poorly, and required large doses of digitalis for severe left heart failure. Autopsy findings in one animal eight months postoperatively revealed an anastomosis 8 mm. in diameter, marked dilatation, and hypertrophy of the left side of the heart (left ventricular myocardium 11 mm., right, 3 mm.). Dogs with a small anastomosis behaved relatively normally. Autopsy findings in one animal killed eight months postoperatively revealed mild left ventricular hypertrophy (7 mm., right, 3 mm.) and an anastomosis 1 to 2 mm. in diameter.

Serial lung biopsies were examined, and the total diameter, thickness of each layer of wall, and diameter of the lumen of 20 or more arteries and veins in each section were measured accurately. The ratio of media and intima to the size of the lumen was determined. In the left lung of dogs with a large anastomosis and severe left heart failure, there was a progressive decrease in lumen size and increase in hypertrophy of the media plus some early intimal thickening of the small muscular arteries. The wall-to-lumen ratio decreased progressively. In both lungs there was marked thickening of the walls of the veins. Arterial and venous changes were minimal in dogs with a small anastomosis.

These experimentally produced arterial changes are similar to those changes found in patients with arteriovenous shunts. A review of lung biopsy material and wall-to-lumen ratios from patients operated upon for congenital heart disease indicate a parallel relationship between the size of the defect and magnitude of pulmonary arterial change. The venous changes resemble those found in patients with long-standing mitral stenosis.

DISCUSSION

Dr. Helen Taussig, Baltimore: Dr. Dammann's paper is very interesting and a very nice piece of work. Certainly the question of pulmonary hypertension is very much in the fore and very important in congenital malformations. We are interested in it, too, and I think we have seen a number of them. I believe there are a number of causes of pulmonary hypertension.

Follow-up studies on one of our patients with a large ductus and pulmonary hypertension showed distressing results after ligation of the ductus. Although there was great clinical improvement, cardiac catheterization revealed that the pulmonary hypertension had increased. I should like to know if Dr. Dammann's baby has been recatheterized to determine whether the pressure has come down.

Dr. J. Francis Dammann Jr., Santa Monica, Calif.: The child has not been recatheterized. I should like very much at some future date to obtain a lung biopsy. Our hope is to show that these changes are reversible by reversing the pulmonary circulation back to normal in this series of dogs. This, of course, is going to be difficult, and we don't plan to do it until the changes have became extremely marked. I am not sure whether it is physically possible. Their chests have been opened many times, and whether we can dissect out the anastomosis and return the left pulmonary artery to the main pulmonary artery is indeed a question.

In the few instances of single ventricle in which pulmonary stenosis has been created, there was a high pulmonary artery pressure and marked vascular changes similar to the ones I have shown were present.

In a few patients we have obtained postoperative biopsies and have shown an increase in the lumen size and a decrease in the arterial thickening. Pressures beyond the point of stenosis are low now.

Studies in Humoral Thromboplastins. Dr. Julius Rutzky, Shirley A. Johnson, Ph.D., and Dr. Wolf W. Zuelzer, Detroit.

Utilizing purified prothrombin and fibrinogen, workers in Seeger's laboratory demonstrated thromboplastin activity in normal plasma in the presence of platelet fragments. A lesser but still significant degree of activity was found in serum. In further studies by the same method, we showed that in hemiphilia the serum thromboplastin activity is intact, but in contrast to the normal, the activity of hemophilic plasma is no greater than that of normal or hemophilic serum. The defect in hemophilia may thus be characterized as lack of plasma thromboplastin activity. The separate identity of this activity was suggested by the following experiments.

Platelet-free plasma was obtained from a hemophiliac whose coagulation defect was refractory in vitro and in vivo to correction by fresh normal blood or plasma and who was shown to have a circulating anticoagulant. By adding the patient's plasma in varying dilutions to normal plasma, using purified reagents, it was shown that the anticoagulant effect consisted in the complete neutralization of the normal plasma thromboplastin activity in dilutions as high as 1:4. Although the anticoagulant was many times more concentrated in one experiment than in another, it never affected the activity in the range of normal serum. The normal plasma, after treatment with the patient's plasma, thus behaved like hemophilic plasma. This study indicates a qualitative difference between the normal plasma activity and the thromboplastin activity found in serum without resorting to coagulation for the demonstration of the serum level.

The significance of the serum activity was demonstrated in a second patient whose manner of bleeding and family history suggested hemophilia but whose blood had a consistently normal prothrombin time, prothrombin consumption, and coagulation time. In contrast to experience with 13 consecutive typical hemophiliac patients, the plasma-serum difference in thromboplastin activity was preserved in this patient, but both plasma and serum values were greatly reduced, the serum value being well below that of both normal and hemophilic serum. This case illustrates the clinical and physiologic significance of a serum thromboplastin demonstrable with this method. The fact that even in this patient residual serum activity was present suggests the existence of more than one type of serum thromboplastin activity.

Dr. Irving Schulman, New York: I should like to compliment Dr. Rutzky on this piece of work, and I think it is absolutely fitting that the pediatrician is becoming more and more interested in the problem of coagulation. So many of these hemorrhagic diseases are familial, congenital, or hereditary that they must frequently come to the attention of the pediatrician first. We are frequently confronted with these enigmatic cases where they look like hemophiliacs and where tests do not show them to be so. Dr. Rutzky seems to have presented us with a new diagnostic tool, which may aid us in separating the diseases.

It has been shown previously that when the first bit of thrombin is formed, various accelerator systems are set in motion. I am speaking in terms of those that are thought to be in the form of platlet labelizers. The whole process is accelerated back in the first phase again when the first bit of clot appears. Does Dr. Rutzky have any evidence to negate the fact that his serum acts as an accelerator? I know, of course, from the data that the platelets were broken down. I wonder whether he has any evidence as to whether this may act in some way in combination with the platelet factor, be it enzyme or not.

DR. JULIUS RUTZKY, Detroit: As ordinarily performed, the essay procedure would probably not detect the contribution of the patient's own platelets to the serum curve, inasmuch as a considerable excess of bovine platelet substance is introduced in each run. The method has also been adapted to assay platelets.

PAPERS READ BY TITLE

Treatment of Heavy Metal Poisoning with Disodium Calcium Ethylene Diamine Tetraacetate (Ca EDTA). DR. J. B. SIDBURY JR., Atlanta, Ga.

Ethylenediamine tetraacetic acid is an organic compound which chelates di- and tri-valent metal ions, resulting in a virtually nonionized metal complex. The calcium chelate has been used in the present study to obviate undesired calcium demineralization and possible tetany consequent to chelation of body calcium. Ca EDTA is not concentrated in any organ or tissues of the body, and it is rapidly excreted by the kidneys. No toxicity has been encountered with its administration to 23 patients in amounts not to exceed 30 mg. per kilogram of body weight per dose.

Thirteen patients, 2 children and 11 adults, with evidence of excessive lead ingestion have been treated with Ca EDTA parenterally, orally, or alternately by both routes. In all instances urinary lead excretion was significantly increased (fivefold to sixtyfold) and a reduction of the concentration of the blood lead resulted. Those patients with symptoms of plumbism were promptly relieved.

Four patients with mercury poisoning were treated with Ca EDTA: (1) a 28-year-old adult with skin, central nervous system, and renal involvement resulting from chronic mercury poisoning, (2) an 8-month-old infant with acrodynia, (3) a 3-year-old boy with acute mercury poisoning following the ingestion of 1.0 gm. of bichloride of mercury, (4) a 5-year-old boy who ingested 0.5 gm. of mercuric chloride. The two cases of chronic mercury poisoning cleared promptly, the latter after failing to show a satisfactory clinical response to dimercaprol (BAL). The older boy with acute mercury poisoning recovered without evidencing severe symptoms. In the younger boy massive albuminuria and transitory emesis, diarrhea, oliguria, and azotemia developed. The unusually benign course observed in the acute cases can probably be attributed to the institution of therapy with Ca EDTA within two hours after ingestion of the mercury.

Ca EDTA did not seem to be effective in eliminating excessive body stores of iron or radium. A 4-year-old boy with congenital refractory anemia, the recipient of multiple transfusions, was given a 5-day course of Ca EDTA without effecting a reduction of the serum-iron concentration or producing an increase in his urinary iron excretion. One radium-dial painter with a breath sample for radon of 0.6×10 to 12 mc. failed to show any radioactivity in the 24-hour urine specimens as a result of treatment with Ca EDTA.

The Use of Dextran in the Nephrotic Syndrome. DR. JOHN A. JAMES, DR. D. J. CONWAY, DR. G. GORDILLO, and DR. JACK METCOFF, Boston.

The relationship between plasma volume, filtration rate, proteinuria, and diuresis has been studied by infusing dextran, a complex polysaccharide having an average molecular weight of 70,000, into a group of 10 nephrotic children. With each infusion a prompt rise in urine volume occurred, resulting in many instances in loss of weight and clinical improvement. Three children lost all their edema fluid, and partial diuresis occurred in five. Two children failed to respond. No toxic effects of therapy were observed, although transient hypertension occurred in several instances.

Measurements of serum and urine albumin and total solute concentrations were made. Plasma volume and renal function were measured. The results show that dextran produced a marked increased in effective plasma volume. Urine volume increased tenfold, and the solute concentra-

tion fell markedly below that in the plasma, indicating a water diuresis. The serum-albumin level fell during the infusion, while albumin excretion remained the same or increased, defining a slight rise in albumin clearance.

Dextran, therefore, may prove to be a useful diuretic in the nephrotic syndrome, producing an immediate water diuresis, in contrast to the usual type of diuresis occurring in nephrotic patients. The filtration of albumin and of H_2O did not change significantly. Dextran appears to act by decreasing water reabsorption, presumably due to a decreased effect of antidiuretic substances. This mechanism is under investigation and will be discussed.

Clinical and Hemodynamic Studies of Congenital Pulmonic Stenosis with Intact Ventricular Septum. Dr. Howard A. Joos, Dr. Paul N. G. Yu, Dr. Frank W. Lovejoy Jr., Dr. Robert E. Nye Jr., and John H. Simpson, Rochester, N. Y.

Nineteen proved and five probable cases of congenital pulmonic stenosis with intact ventricular septum are reported. Symptoms were generally infrequent, inconspicuous, and without relation to the magnitude of right ventricular hypertension. The intensity of the systolic murmur was not grossly related to the severity of pulmonic stenosis. The valvular type was characteristically associated with a murmur in the second left interspace. Apparent left ventricular enlargement seen by x-ray in 11 cases was confirmed by electrocardiographic evidence of unexplained left ventricular hypertrophy in only two instances. Excercise tolerance as reflected by the physical fitness index was unrelated to the severity of pulmonic stenosis. Marked tachycardia during exercise suggested that cardiac output under stress may be augmented by a relatively greater increase in heart rate than stroke volume. The infrequency of paradoxical responses suggests that pulmonary artery flow is increased during exercise, although in certain cases the increment may be limited by restriction of right ventricular outflow. The usually normal mean pulmonary artery pressure witnesses the adequacy of compensatory right ventricular hypertension at rest. Right ventricular systolic hypertension and the gradient between right ventricular and pulmonary artery systolic pressure were grossly related to the occurrence of right ventricular hypertrophy by electrocardiogram. Pulmonic stenosis did not interfere with cardiac output at rest. The volume of right-to-left shunt in eight cases was unrelated to right ventricular hypertension. Cross sectional area of flow of the pulmonic valve varied inversely with resistance, which was reflected, in turn, by increased values for right ventricular work. The physiologic handicap and resulting reduction in cardiac reserve suggest the possible advantage of surgical correction, even of mild cases.

Observations on Vitamin A Absorption in the Allergic Celiac Syndrome. Dr. Douglas E. Johnstone and Augusta McCoord, Rochester, N. Y.

The differences in ability to absorb vitamin A alcohol and vitamin A ester constitute a basis for differentiating cystic fibrosis of the pancreas from other forms of the celiac syndrome. Children with idiopathic celiac syndrome do not absorb either form of vitamin A well, due to an incompletely understood defect in intestinal absorption. Children with pancreatic deficiency, however, absorb the alcohol form of vitamin A well, since they have no abnormality of absorption. They can not, however, absorb the ester of vitamin A, which requires the presence of a lipase to saponify this form before it may be absorbed.

Three children with a celiac syndrome on an allergic basis showed a hitherto unreported peculiarity of vitamin A absorption. Their vitamin A absorption curves strikingly paralleled those of infants with cystic fibrosis of the pancreas. They fulfilled every accepted clinical and laboratory criterion for the diagnosis of cystic fibrosis of the pancreas except that their duodenal juice enzyme concentrations and viscosity were normal. When the nature of their disorder was properly ascertained and the offending allergen had been withdrawn from their diets, the clinical and laboratory findings approached normal. The laboratory and clinical evidence for the existence of the celiac syndrome in these children will be presented. It is hoped that study of this entity may help to elucidate the pathological process in true idiopathic celiac disease as well as to justify further attempts to reclassify some cases of idiopathic celiac disease which have been improperly diagnosed.

Psychogenic Megacolon with Encopresis as a Specific Syndrome. Dr. Julius B. Richmond, Ann Magaret, and Dr. Evelyn Eddy, Chicago.

The demonstration by Swenson and others that congenital megacolon is secondary to partial large intestinal obstruction as a result of a congenital neurogenic defect of the colon has reawakened interest in this disorder. The development of an effective surgical therapy for this disorder has rendered specific diagnosis of considerable importance.

In recent studies a syndrome of psychogenically determined megacolon associated with fecal retention and often fecal soiling (encopresis) has been noted. These patients may be differentiated from those with neurogenic megacolon by careful clinical evaluation and radiologic findings. These differences will be presented in tabular form. As a result of the clarification of cause in these two forms of megacolon all cases of megacolon should fit into one of the following three groups: (1) neurogenic (aganglionic) megacolon, (2) psychogenic megacolon, and (3) anatomic megacolon.

To elucidate the nature of the psychological problems in the psychogenic group a methodological approach to the study of mother-child interaction was developed employing identical psychometric techniques for mother and child. As might be anticipated from the nature of the symptoms, the patients revealed themselves on these techniques as somewhat infantile and immature and as passive in their overt orientation to others. More profoundly, however, many of these children are involved in hostile destructive fantasies, although in some cases even this emotional expression is absent and, indeed, possibly deeply repressed.

The mother participated in the same psychometric procedures as did their children so that item-for-item comparisons between the responses of child and mother could be made. In general, these mothers reveal themselves as emotionally impoverished and lacking adequate emotional resources on which to draw in their relationships with their children. There are some impressive instances in which, in their response to psychometric stimuli, the children reveal a deep need for emotional response from the mother—a need which the mother, judging from the same psychometric stimuli, is unable to meet. The resulting picture of mother-child interaction is one of distance and mutual frustration.

Hypertension in Poliomyelitis. Dr. Harris D. Riley Jr. and Dr. Randolph Batson, Nashville, Tenn.

During the period of these observations, 140 poliomyelitic patients were hospitalized. Blood pressures were recorded at least twice daily and more often when indicated. For purposes of this study, we recorded not the highest blood pressure obtained but the lowest blood pressure recorded during the 48-hour peak of the hypertensive phase. Many hypertensive and normotensive patients did not qualify for this study because they did not have blood pressure determination over a continuous 48-hour period.

A total of 77 patients did qualify for this study, and, of this group 49 patients, or 63.7%, had hypertension by what we considered rather rigid criteria. This may be further broken down into the various types of involvement as follows:

	Nonparalytic	*Paralytic (Nonbulbar)*	*Bulbar*
Total patients	7	39	31
No. hypertensive	4	15	30
Per cent hypertensive	59	38	93.6

Cases illustrating the course of hypertension during hospitalization will be used showing the response or failure of response to hypertensive drugs. Also determination of nonprotein nitrogen, calcium, phosphorus, urinary findings, and Addis tests are to be included.

Due to the paucity of information on hypertension in poliomyelitis, we have attempted to demonstrate the frequency of hypertension in this disease. It is not yet an attempt to explain the mechanism of hypertension in poliomyelitis, even though many of the common tests for renal function have been performed, and hypotensive drugs have been given as a therapeutic trial. Rather it is to emphasize the high incidence of hypertension in poliomyelitis and the complication incurred as a result.

Growth and Development of Negro Infants: IV. Motor Development and Its Relationship to Child Rearing Practices in Two Groups of Negro Infants from Different Socioeconomic Classes. Dr. Judith Williams and Dr. Roland B. Scott, Washington, D. C.

The study summarized below was undertaken as a follow-up of a previous investigation in which the development of a group of white and Negro infants was compared by means of the Gesell Developmental Schedules and in which the Negroes displayed acceleration of gross motor behavior.

The present study postulates that the pattern of motor development, accelerated or otherwise, is not a "racial" characteristic, but, instead, related to the manner in which an infant is handled and cared for. Since rearing practices have been shown to vary with socioeconomic class, the subjects for this study, although all Negroes, were selected from two sharply contrasting socioeconomic backgrounds.

The gross motor items of the Gesell Development Schedules were administered to 104 infants ranging in age from 4 to 18 months. The infants were seen a second time in their own homes. Detailed observations were made and recorded on the interaction between child and mother or mother-substitute. A nondirective interview was conducted which covered various areas of child care, mainly those aspects of care which were felt to have a direct bearing on motor development.

The results were as follows: The infants from the low socioeconomic group showed significant gross motor acceleration when compared to those from the high socioeconomic group. Significant differences were also found for the ways in which the infants of the two groups were handled. Specific practices, as well as the over-all home atmosphere, were more permissive and less exacting among families of the low socioeconomic group. Differences in motor development were found to be related to methods of child care with infants from permissive accepting environments scoring significantly higher on the Gesell Developmental Schedules than infants from rigid rejecting environments. The findings of the study suggest that motor acceleration is in no way a "racial" characteristic.

Preliminary Observations on Plasma Protein Changes in Nephrotic Children Treated with Ten Percent Salt-Free Dextran and Gelatin. Dr. Robert A. Aldrich, Dr. Anne Perley, and Dr. Tyra Hutchens, Portland, Ore.

The intravenous administration of 10% salt-free dextran or gelatin to nephrotic children with massive edema has resulted in a striking reduction of the edema in all patients treated so far. During the therapeutic period a marked reduction has been noted in the total plasma protein. This decrease is reflected in both the albumin and globulin fractions. In one person the total plasma protein fell to 32% of the pretreatment level following the administration of 225 gm. of dextran over a period of nine days. On another occasion in this same patient, the serum proteins fell to 46% after injection of 300 gm. of gelatin over a period of seven days. When intravenous therapy is discontinued, the serum proteins gradually return to the pretreatment level.

An effort has been made to investigate certain mechanisms which might contribute to these changes. Expansion of plasma volume has been studied using radioiodinated serum albumin. In addition, the rate of protein loss through the kidney has been investigated prior to, during, and after the administration of dextran. The observations on plasma volume were carried out at least 18 hours after the last dextran infusion. In one patient, at a time when the plasma proteins were found to be 50% of the initial value the plasma volume measured 109% of the pretreatment figure. Later, with continued dextran administration, the proteins had fallen further to 32%, and the plasma volume at this time was 111% of the pretreatment level. In a second patient, when the plasma protein had been reduced to 54% the plasma volume was found to be 114% of the average pretreatment figure. When it had fallen still further, to 45%, with continued dextran administration, the plasma volume as measured was practically identical with the pretreatment value. In this last patient, urinary excretion of protein was followed for several weeks prior to and during dextran administration. No increase in excretion of protein was observed during the period of administration of dextran.

We wish to present preliminary observations which seem to indicate that the fall in total plasma protein under these circumstances cannot be explained on the basis of plasma volume dilution or of increased protein excretion by the kidney. Some of the implications which arise from these observations will be discussed.

Metabolism of Lauric Acid as Compared to Palmitic Acid in the Normal and Hypophysectomized Rat. Dr. Samuel Spector, Dr. Lee W. Matthews, Paul Olynyk, and F. J. Lemm, Cleveland.

In the normal rat, lauric acid, a 12-carbon fatty acid, is handled differently than the longer-chain fatty acids, such as palmitic acid, which predominate in the blood depots. Although it has been shown by others that lauric acid can be synthesized to a longer-chain fatty acid as well as oxidized, our work indicates that the direction of the reaction is such that lauric acid is predominantly oxidized. In six hours, 60% of the lauric acid is utilized, as compared to 26% of the palmitic acid. By clearance study, it has been shown that whereas palmitic acid rapidly enters fat depots, lauric acid awaits oxidation or synthesis. Also, there is a rapid turnover of fat from depots as indicated by continued utilization of palmitic acid after its clearance to low level in the blood.

Hypophysectomy in the rat reduces utilization and deposition of palmitic acid. Pituitary growth hormone administered to the hypophysectomized rat increases fat utilization.

Dehydroepiandrosterone in the Urine of Premature Infants. Dr. J. Frederick Eagle and Dr. Charles Upton Lowe, Buffalo.

Dehydroepiandrosterone (DHA) is an androgenic 17-ketosteroid which appears in the urine of normal mature persons. It is derived from the adrenal gland, rather than the testis or the ovary. In patients with adrenal carcinoma DHA or DHA-like substances are excreted in the urine in increased amounts relative to total 17-ketosterone excretion, so that when the extracted steroids are heated with alcoholic H_2SO_4 a blue color (a positive "blue test") is produced. A positive blue test is considered to be almost diagnostic of adrenal carcinoma in older persons.

It has been suggested (Eagle: *Proc. Soc. Exper. Biol. & Med.*, 1952) that adrenal steroid metabolism in the premature infant is qualitatively different from that of the mature person, because the blue test is frequently positive in premature infants who are otherwise normal.

The purpose of this study was to investigate the DHA excretion of premature infants in response to adrenal stimulation. When Acthar Gel (corticotropin in gelatin and propylene glycol) was given subcutaneously over a two-day period, the 17-ketosteroid excretion always increased. The blue test always became positive. It was found that the increase in total 17-ketosteroid excretion could be almost entirely attributed to an increase in DHA or DHA-like substances, a finding consistent with similar observations made by Landau on adults.

The reason for a positive blue test in this age group and under these circumstances is not clear, but could be explained by variations in (1) steroid secretion by the adrenals, (2) intermediary steroid metabolism, and/or (3) renal steroid excretion. From these studies, one might also conclude that the premature infant can respond to adrenal stimulation by excreting increased amounts of DHA in a manner that is comparable to the adult.

Studies on the Physical and Physiological Properties of Saliva of Children with Cystic Fibrosis of the Pancreas. Dr. Douglas E. Johnstone and Augusta McCoord, Rochester, N. Y.

A study of various properties of the saliva of children with pancreatic deficiency was undertaken to ascertain any possible abnormalities in salivary function which might shed light on the mucoviscidosis theory of this disorder.

Fasting saliva specimens from 15 children with cystic fibrosis of the pancreas, 12 normal children and three children with idiopathic celiac disease, were studied. The following data were obtained on these specimens: (1) amylase, (2) viscosity, (3) chloride concentration, (4) potassium concentration, (5) sodium concentration, (6) buffering capacity, and (7) titratable acidity. In addition, the reports of their dental examinations were compared with their salivary lactobacilli counts.

The comparative results from the three groups will be discussed. The data suggest that children with cystic fibrosis of the pancreas do not have mucoviscidosis of their salivary glands. The possible relationship of the high salivary chloride concentrations in children with congenital pancreatic deficiency to their chronic respiratory acidosis will also be discussed.

Intracardiac Left-To-Right Shunts with Mild Pulmonic Stenosis. Dr. Abraham M. Rudolph, Dr. Alexander S. Nadas, and Dr. Walter T. Goodale, Boston.

In recent years, significant advances in the surgical treatment of patients with cardiac shunts or stenotic lesion have been made. In the course of studies aimed at selection of candidates for surgery, a physiological syndrome, combining the features of intracardiac left-to-right shunts with those of pulmonic stenosis, has been encountered.

The characteristic clinical features and the physiology in six cases of atrial septal defect and pulmonic stenosis and three cases of ventricular septal defect and pulmonic stenosis are described. Patients in both groups showed cardiac enlargement and pulmonary vascular engorgement. The electrocardiograms uniformly showed right ventricular hypertrophy. The physical findings combined the features of the individual defects. Catheterization data showed significant left-to-right shunts in all instances and lesser degrees of right-to-left shunt in three cases of atrial septal defect. The degree of pulmonic stenosis was appreciable in all cases, but not significant enough in any instance to abolish the left-to-right shunt.

This entity is presented as a clinically well defined and hitherto not clearly recognized congenital heart syndrome. The present group of patients is large enough to permit consideration of the surgical significance of the individual defects.

An Evaluation of Iron Absorption in Infants and Children. Dr. Nathan J. Smith, Dr. Salvador Rosello, and Dr. Kazuko Yeya, Philadelphia.

The absorption of iron from the gastrointestinal tract in infants and children has been studied by using iron-absorption curves. In each experiment the fasting serum iron level was determined, after which a measured amount of ferrous iron was given orally in aqueous solution. The serum iron level was then determined at hourly intervals for four or five hours.

In an attempt to evaluate the effect of several factors on the absorption of iron, 175 subjects, 1 month to 14 years of age, have been studied with this technique. The following factors have been evaluated as to their effect on iron absorption: (1) age, (2) iron deficiency, (3) iron excess as seen in hemosiderosis, (4) anemia in the absence of iron deficiency or iron excess, (5) abnormalities of the gastrointestinal tract, (6) chemical form of the ingested iron, and (7) various food factors.

There are certain limitations to this method of study, since the results are in no way quantitative. However, the results have been interpreted in conjunction with those of quantitative studies using radioactive iron. It is concluded that certain aspects of the absorption of iron can be successfully studied by the use of iron-absorption curves and that these are affected by many factors.

Chemical Control of Respiration in Newborn Infants. Dr. Bruce D. Graham, and Dr. James L. Wilson, Ann Arbor, Mich.

This report is concerned with the measure of the major stimulants to respiration in the blood of the newly born infant and includes a discussion of the variability of these stimulants (hypoxia, blood pH, and plasma CO tension) and of the shifting impetus for control of respiration in the newborn infant.

In a study of 64 full-term infants, an average blood pH of 7.33 occurred at birth and rose to 7.43 by 4 hours of age, with no change in the total plasma CO_2 content (19.7 to 19.9) during the first day of life. There was, however, a decisive drop in CO_2 tension of 5 mm. of Hg (35 to 30) during this time and a rise in blood oxygen saturation from 85% at birth to 91% in the few hours succeeding birth.

The more recently and generally accepted concepts of the control of respiration are discussed briefly in light of the above findings.

The CO_2 tension at birth is below the level of stimulation in a normal adult and falls during the first day, indicating CO_2 tension is being driven to a lower level by some factor other than itself. Blood pH as a stimulant is discussed both as to its strength and point of action. These infants adjust to a "normal" pH with a lowered CO_2 tension without evidence of extreme ventilation. Data are shown to indicate that this may well correlate with initially high plasma levels of other organic acids which fall concomitantly with the establishment of a normal pH.

The oxygen saturation and oxygen tension at birth should elicit intense and effective hyperpnea by adult standards. It is suggested that perhaps in some of these infants a teeter-board action may occur in respect to oxygen tension and pH levels regulating the periodic breathing.

The data indicate a great variability of chemical stimuli to respiration in the blood of the newly born infant. In some instances, at least, there are indications that a considerable portion of the total stimulus to respiration may be mediated through the chemoreceptors of the carotid and aortic bodies, rather than through the respiratory center per se, at least until the homeostatic state of adult equilibrium is reached during the first day of life.

A New and Readily Available Test for Accelerator-Globulin Activity. Dr. William S. Downey Jr., Boston.

Accelerator globulin is one of the more important recently discovered factors concerned with blood coagulation. It has been shown essential in the normal conversion of prothrombin to thrombin. Its activity is lost from plasma by just standing and, in fact, the most widely used method for measuring it in patient's plasma is the ability of the patient's plasma to lower the prothrombin time of stored ("accelerator-globulin free") plasma toward normal. However, the present method requires the storing of the plasma for three to four weeks before it is accelerator-globulin free and thus is generally available only to research laboratories set up to study blood coagulation. A new method has been devised by which the plasma used for the test can be made accelerator-globulin free in three to four hours, and thus any laboratory where one-stage prothrombin tests can be done will also be able to run a test for accelerator-globulin activity. Congenital accelerator-globulin deficiency is rare, but patients with severe liver disease have been shown to have a deficiency of it. Reports of accelerator-globulin deficiency in other conditions are appearing in the literature now.

It is impossible to distinguish hypoprothrombenemia from a deficiency of accelerator-globulin on the basis of the one-stage prothrombin test alone, but yet it is important to distinguish between these two conditions since the former responds to vitamin K therapy as a rule but the latter requires fresh plasma. Thus, the value of having a test for accelerator-globulin activity readily available for clinical use exists.

The Effect of Ascorbic Acid Administration on Adrenal Function. Dr. R. Klein and Dr. C. Papadatos, Pittsburgh.

Bacchus and co-workers have reported that the 17-ketosteroid excretion of rats diminishes when the rats are given ascorbic acid. In addition, these authors have suggested that the ascorbic acid potentiates the action of exogenous steroids.

Ascorbic acid in large doses has therefore been given to humans. Chemical estimations of 17-ketosteroids and 11,20 oxysteroids and bioassay of androgens were carried out on urines before, during, and after administration of vitamin C. During the same periods blood levels of 17-hydroxycorticosterone-like (Compound-F-like) materials were measured and eosinophile counts were made.

Ketosteroid excretion fell upon administration of the vitamin, as it had in the rat. An attempt will be made to explain this on the basis of the changes in 11,20-oxysteroid excretion, blood levels of 17-hydroxycorticosterone, and lack of changes in androgen production.

Effects of Salicylate Administration on Circulating 17-Hydroxycorticosteroid Concentrations. Dr. Robert S. Ely, Dr. Alan K. Done, and Dr. Vincent C. Kelley, Salt Lake City.

Several investigators have commented upon the similarity of the physiologic effects observed in response to corticotropin (ACTH) or cortisone and to salicylates. Because of this evidence combined with indirect chemical evidence stimulation of the adrenal cortex by salicylates has been postulated. The recent demonstration that in man the principal adrenal steroid is 17-hydroxycorticosterone and the development of a reliable chemical technique for estimating plasma concentrations of 17-hydroxycorticosteroids have made possible more definite study of the relationship between salicylates and adrenal cortex steroids. This report is concerned with the effects on circulating 17-hydroxycorticosteroid concentrations, in man and animals (determined by the method of Nelson and Samuels), of salicylates in various doses.

Patients with salicylate intoxication observed in this study uniformly exhibited marked elevations of 17-hydroxycorticosteroid concentrations. Likewise, guinea pigs given large single doses of salicylates had similar elevations. However, only 50% of control human subjects given massive salicylate doses showed significant elevations of 17-hydroxycorticosteroids, despite adequate eosinopenic response in two-thirds of these persons. Increases in 17-hydroxycorticosteroid concentrations were not observed in any persons whose plasma salicylate levels were less than 25 mg. per 100 ml. At plasma salicylate concentrations greater than 25 mg. per 100 ml. increases in steroid concentration were observed frequently but not consistently, but no consistent correlation with salicylate concentration or absolute eosinophile count was apparent.

A consistent decrease in steroid level, compared to normal diurnal fluctuations on control days, occurred in subjects given low doses of salicylates and during the initial period following the administration of large doses. Following this initial decrease, significant elevations occurred in most of those subjects in whom high salicylate levels developed. In subjects receiving repeated doses of salicylates extreme fluctuations of the 17-hydroxycorticosteroid concentrations occurred.

Urinary excretion of 17-hydroxycorticosteroids does not play a role in bringing about the observed decreases in plasma concentrations, since in all periods of study following salicylate administration the urinary excretion of 17-hydroxycorticosteroids was less than during corresponding periods on control days.

A possible explanation of the data obtained might be that salicylates cause increased peripheral utilization or destruction of 17-hydroxycorticosteroids and that in high doses they also cause an increased secretion of these steroids by the adrenal cortex. This and other possible explanations will be discussed. Animal experiments designed to clarify the interpretation of these data are in progress.

Aseptic Meningitis and Short-Term Fevers in Childhood: Observations on Outbreaks in Ontario, Summer 1952, with Particular Reference to the Role of Coxsackie Viruses. Dr. A. J. Rhodes, Dr. W. Wood, Dr. C. C. R. Johnson, Dr. G. A. McNaughton, and Dr. Nelles Silverthorne, Toronto, Canada.

During the summer of 1952 there were several outbreaks of short-term febrile illnesses, some with aseptic meningitis, in southern Ontario communities. Of particular interest was the situation in the city of Toronto, where between July and November there were admitted to the Hospital for Sick Children approximately 80 patients with a clinical diagnosis of nonparalytic poliomyelitis (aseptic meningitis); during the same period only 20 patients were admitted with a clinical diagnosis of paralytic poliomyelitis. Laboratory investigations have been carred out on many of these nonparalytic patients; tissue cultures, monkeys, and suckling mice have been inoculated, and serological tests have been performed. The results suggest that in several patients suffering from aseptic meningitis Coxsackie viruses (Group B) played an important role; many such strains were isolated, whereas only a few poliomyelitis viruses were recovered. Of additional interest was the outbreak that occurred in the city of Brantford, where over 2,000 of the 20,000 inhabitants were affected by a febrile illness, aseptic meningitis being present in some patients. Strains of virus pathogenic for suckling mice and resembling Coxsackie viruses have been recovered from some of these patients. Observations made in 1952 and earlier years point to the role played by Coxsackie viruses in pyrexial illnesses of childhood in the summer months.

Gastrointestinal Lavage in the Management of Hyperpotassemia Associated with Kidney Failure. Dr. H. W. Bain, Toronto, Canada.

A simple method of management of hyperpotassemia in renal failure is presented.

Gastrointestinal lavage is performed by means of an ordinary duodenal tube, with a rectal tube serving as the afferent pathway.

Four and one-half per cent sodium sulfate was used as the perfusing fluid.

Twenty-five hundred cubic centimeters of this fluid, run in over a 15-hour period, accomplished the following: (*a*) a moribund semicomatose patient was restored to a fully conscious state, lived for a further three weeks, and was able to undergo operation for removal of a kidney stone impacted in the ureter. Death was due to oxalosis with chronic kidney failure as reported in *Pediatrics*, Dec., 1952; (*b*) generalized edema and ascites was considerably reduced as a negative water balance resulted: intake by intravenous (10% dextrose in an oil and water emulsion)

and intestinal lavage, 3,400 cc.; output by urine and stool 4,000 cc.; (*c*) serum K was reduced from 9.6 mEq. per liter to 2.9 mEq. per liter; ECG changes paralleled the serum K changes; (*d*) nonprotein nitrogen was reduced from 234 mg. per 100 cc. to 180 mg. per 100 cc.; (*e*) serum Na rose from 125 mEq. per liter to 156 mEq. per liter; (*f*) serum Cl remained unchanged at 100 mEq. per liter; (*g*) serum Ca dropped slightly from 8.8 mg. per 100 cc. to 8.3 mg. per 100 cc.; (*h*) serum phosphate and creatinine were essentially unaltered, remaining at levels of 16 mg. per 100 cc. and 12.1 mg. per 100 cc., respectively; (*i*) abdominal distension did not occur; a few mild abdominal cramps occurred, but these were not a major feature; (*j*) once established, fluid dripped from the rectal tube almost as quickly as it ran in.

Although it is impossible to draw further conclusions as to what the dialysis accomplished in this case of uremia due to chronic kidney failure, certainly it is a useful and simple method of reducing serum K and may be of value in the treatment of this complication as it arises in acute kidney failure associated with lower nephron nephrosis.

The Frequency and Nature of Hypertonicity of the Body Fluids in Infantile Diarrhea. Dr. Robert Tarail, Dr. Lee W. Bass, and Angelo S. Runco, Pittsburgh.

Significant elevation in concentration of serum sodium has been regarded usually as a rare finding in infants with severe diarrhea. Programs of parenteral replacement therapy, therefore, emphasize use of sodium salts as soon as administration of fluids is begun to institute correction of estimated net deficits of sodium, chloride, or bicarbonate immediately. The following data, however, support the thesis that, at least in this clinic, knowledge of concentration of serum sodium, or of tonicity of plasma, contributes to determining the optimal composition of the fluid prescription.

Acute diarrhea was a major factor in the hospitalization of 191 infants and children during a consecutive 13-month period. Serum sodium exceeded 149 mEq. per liter in 21 patients (11%), 154 mEq. per liter in 17 (9%), and 159 mEq. per liter in 14 (7%) upon admission to hospital and prior to fluid therapy. Initial serum chloride was greater than 109 mEq. per liter in 33 (17%), and exceeded 119 in 23 (12%).

Clinical and chemical features of the hypertonic (hypernatremic) group included, in general, severe diarrhea and dehydration, acidosis, and nitrogen retention. Ages ranged from 2 weeks to 16 months (mean, 7 months). Of the 21 with hypernatremia, 5 had received relatively large quantities of sodium salts prior to admission, but such intakes were not recognized in the other 16. There was no evidence of primary renal insufficiency, diabetes insipidus, or adrenal disease; sulfonamide intoxication and antecedent central nervous system disturbance may have occurred in a small fraction. Although vomiting occurred in a portion of the patients, significant elevation of serum sodium was rarely attributable to vomiting without diarrhea during this 13-month period. Putty-like or plastic consistency of the skin was an inconstant correlate of hypernatremia.

All patients with hypernatremia had hyperchloremia, but the converse did not obtain. When in 29 instances serum chloride exceeded 110 mEq. per liter, eight of 29 serum sodium values were below 150 mEq. per liter. This contrasted to consistent striking elevation of serum sodium when serum chloride exceeded 122 mEq. per liter.

Serum potassium, in the 21 infants with initial hypertonicity, varied from 2.8 to 6.7 mEq. per liter (mean 4.7); serum potassium exceeded 4.9 mEq. per liter in 9 and was below 3.6 mEq. per liter in 3. These findings again underlined the need for individualizing fluid prescriptions.

Initial urinary concentrations of sodium, potassium, chloride, and nitrogen and estimates of osmotic pressure of urine will be presented and factors related to expenditure of water in excess of electrolyte assessed.

Preliminary Observations on the Effects of Prolonged Cortisone Therapy upon the Growth of Children with Various Conditions. Dr. F. M. Blodgett, Dr. D. Gribetz, and Dr. N. B. Talbot, Boston.

The possible effects of prolonged orally administered cortisone treatment upon the growth of children are illustrated by data obtained on 7 children selected from a group of approximately 30 currently under study. Height measurements are recorded at frequent intervals before, during, and after the administration of cortisone. Bone age and other pertinent information are given where indicated. All cortisone doses are per square meter of body surface per day.

The data presented show that (1) the rate of growth of a boy with Addison's disease rose from subnormal to normal levels when cortisone was given in physiologic substitution doses (15 mg.); (2) in two hypopituitary patients who were growing at rates of about 5 cm. per year under the influence of thyroid plus testosterone treatment, 10 mg. cortisone doses apparently caused growth to stop; (3) in two representative children with adrenocortical virilism, 25 to 35 mg. of cortisone not only suppressed the hyperketosteroiduria to a considerable extent, but also caused the growth rate to fall from supranormal to low normal or subnormal levels; (4) in two children with severe atopic eczema, the 50 to 100 mg. of cortisone needed to control the skin complaints apparently suppressed statural growth almost completely. At lower cortisone doses, growth was resumed, but the eczema was exacerbated.

It would appear from the foregoing that cortisone is capable of suppressing growth in stature to a marked degree. It remains to be seen whether by suitable adjustments in dosage one can accomplish desired therapeutic effects and at the same time avoid this effect upon growth. The effect of cortisone upon skeletal maturation remains to be determined. This will have an important bearing upon possible relations between prolonged cortisone therapy and ultimate stature.

Choleretic Action of Cortisone. Dr. Paul R. Patterson, Dr. Joseph F. Dingman, and Dr. George W. Thorn, Boston.

Both cortisone and corticotropin (ACTH) have been used in the treatment of infectious hepatitis and allied liver disease. Most observers have noted the elevated serum bilirubin levels were reduced even though liver function tests did not as consistently revert toward normal, nor did clinical improvement always occur.

Inasmuch as the adrenal steroids and cholic acid possess similar chemical configurations, and since cortisone is commercially synthesized from desoxycholic acid, the possible mode of action of these hormones may be that of simple choleresis similar to the action of bile salts upon hepatic biliary flow.

Ten adults and six children received either intravenously or intraduodenally instilled microcrystalline suspension of cortisone acetate. Six additional persons served as controls. The duodenal fluid was analyzed for volume, pH, viscosity, chlorides, bilirubin, icteric index, and enzyme content (trypsin, amylase, lipase, carboxypeptidase, esterase, and phosphatase). A significant rise in volume and/or bilirubins was observed within one hour and again at three to four hours after cortisone.

The pancreozymic-like action of bile upon pancreatic exocrine function is demonstrated by an increase in enzyme activity in a few patients.

Four patients with liver and biliary tract disease responded to the cortisone in this manner.

Correlation of Laboratory and Clinical Signs of Respiratory Insufficiency in Acute Poliomyelitis. Dr. David G. Dickinson, Dr. James L. Wilson, and Dr. Bruce D. Graham, Ann Arbor, Mich.

This study is an attempt to compare the usefulness of laboratory procedures with clinical observation in the detection of early or developing respiratory insufficiency in acute poliomyelitis.

Arterial pH, CO_2 content, CO_2 tension, and hemoglobin saturation were determined on a group of 15 acute-poliomyelitis patients without respiratory paralysis. Thirteen of these showed hyperventilation and were in a state of respiratory alkalosis, presumably from fear. Average arterial CO_2 tension for this group was 30 mm. Hg. None were anoxic.

Similar biochemical measurements were made on a group of 20 acute-poliomyelitis patients in whom sufficient paralysis of their respiratory muscles developed to require a mechanical respirator. At the time that the clinical picture of dyspnea or respiratory insufficiency was well established and obvious, 13 patients were still hyperventilating and in a state of respiratory alkalosis. Four were ventilating normally and only three were in mild respiratory acidosis.

Two of those in respiratory acidosis were transported long distances after they became dyspneic and were studied only after the clinical need for a respirator had been apparent for several hours. These two also had a moderate reduction in hemoglobin oxygen saturation.

Measurements of ventilation were correlated with the biochemical studies and clinical evidence of respiratory insufficiency.

It was concluded that (1) most acute poliomyelitis patients are in a state of respiratory alkalosis; (2) clinically obvious increased respiratory effort, or dyspnea, was successful not only in maintaining adequate pulmonary ventilation but in producing hyperpnea in spite of severe respiratory muscle paralysis; (3) given a normal airway and freedom from intrapulmonary disease, the average poliomyelitis patient will give ample warning of his need for a respirator before damage from anoxia or CO_2 retention occurs.

Serial Serum Cholesterol Values in Children with Diabetes Mellitus of Recent Onset. Dr. Mark S. Dine and Dr. Robert L. Jackson, Iowa City.

Altered lipid metabolism as well as altered carbohydrate metabolism are being emphasized in the study of diabetic patients. In many juvenile diabetic patients who have had their disease over 10 years vascular disease is known to be developing. Inasmuch as these patients are in an age group not expected to have vascular disease and a relationship exists between altered lipid metabolism and atherosclerosis, it is important to determine the interrelationships of level of serum cholesterol, degree of control, and vascular disease in juvenile diabetic patients.

A total of 435 serial serum cholesterol values were determined in 48 children with diabetes early in the course of their disease.

Before insulin therapy was instituted a larger number of elevated values were observed, but there were many values within the normal range. Marked fluctuations in cholesterol values in individual patients were noted, particularly in the early weeks of treatment. The average cholesterol values increase in the first three weeks of therapy and then gradually decrease to a value below the average for normal children. During the period of home management the patients who maintained good control had a relatively constant cholesterol level within the normal range. Patients who maintained only fair to poor control continued to show marked fluctuations in serum cholesterol values. After the period of initial regulation the level of serum cholesterol changed with the degree of control of the disease, not as an immediate response but as a result of weeks or months of a given degree of control. Cholesterol values showed a significant decrease in five patients with mild or severe infection.

This study serves as a base for evaluating the usefulness of various types of therapy and shows the importance of degree of control as a factor in the maintenance of normal lipid as well as normal carbohydrate metabolism.

Hemolytic Disease of the Newborn Due to ABO Incompatability. Dr. Clare N. Shumway and Dr. Gerald Miller, Rochester, N. Y.

Hemolytic disease of the newborn due to ABO incompatibility was investigated in 11 infants in an attempt to establish diagnostic criteria for the disorder.

In all of the infants, jaundice appearing within the first 24 hours of life directed suspicion toward the presence of the disease.

The hematologic findings observed were as follows: (1) spherocytosis of a significant degree in the peripheral blood; (2) a corresponding increase of the osmotic fragility of the red blood cells; (3) reticulocytosis above the accepted limit of normal for this age group; (4) hyperbilirubinemia ranging between 4. and 18.0 mg. per 100 cc.; (5) the presence within the first 24 hours of birth of a mild degree of anemia in only three of the children (Anemia developed during the first week of life in a total of five of the untreated infants and was never severe).

The notable serologic observations were as follows: (1) fetal-maternal incompatibility involving the major blood groups; (2) a negative direct antiglobulin (Coombs) test in 9 of the 11 cases; (3) in 9 of 10 of those tested, the occurrence of agglutination of the baby's whole blood when it was mixed with AB serum on a warmed slide.

Investigation of the mothers' sera revealed nothing of a diagnostic nature. The major blood group antibodies were found to have some of the so-called "immune" characteristics, but no one finding was common to all specimens examined. No irregular isoantibody was demonstrated.

Recognition of this disease depends largely on the demonstration of spherocytosis, increased

osmotic fragility, reticulocytosis, and hyperbilirubinemia in an infant less than 24 hours of age whose red blood cells are incompatible with the maternal major blood group antibody and against whose cells no other maternal isoantibody is demonstrable.

Colorimetric Fractionation of Urinary Ketosteroids in Congenital Adrenal Hyperplasia: The Induction of Qualitative Changes by Treatment with Cortisone and Hydrocortisone. DR. EDNA H. SOBEL, LELAND C. CLARK JR., MARCIA BRUSSEL, and GWEN PRIOR, Cincinnati.

A method being developed in this laboratory distinguishes between classes of ketonic steroids because the reactivity of the ketone group is related to its position in the steroid nucleus. The procedure was used in studying the neutral lipid extract of acid hydrolysed urine collected from an 11-year-old boy who has congenital adrenal hyperplasia with electrolyte imbalance. All results were calculated in terms of dehydroisoandrosterone. It was found that the very high 17-ketosteroid excretion of 112 to 145 mg. per day (Zimmerman) represented only approximately 45% of the total ketonic material excreted (average 290 mg. per day). Twenty-five percent of the total was composed of 3- and 20-ketosteroids, while an unidentified group of ketonic compounds ("X") comprised 30% (75 to 120 mg. per day). Oral administration of cortisone acetate or hydrocortisone (100 mg. daily) resulted in reduction of all the steroids measured to about 20% of the control values ($P = 0.004$). Hydrocortisone acetate in the same dose was apparently less effective ($P = 0.028$), as the steroid excretion rose to 40% of the control value. There were distinct qualitative shifts in the steroid excretion during treatment with cortisone acetate and hydrocortisone, as the 17-ketosteroids (Zimmerman) were reduced to 40% of the total and "X" to 25%, while the relative amount of 3- and 20-ketosteroids increased to 35%. The excretion of "X" rose the most rapidly when treatment was discontinued; at the same time there was an episode of moderate dehydration and electrolyte insufficiency. During the immediate post-treatment period "X" was excreted in amounts almost equal to those of the control period, while the other steroids were still somewhat reduced (75% of the control values).

Quantitative Aspects of Iodine Metabolism In Normal and I^{131} Thyroid-Ablated Infant Rhesus Monkeys (Macaca Mulatta). DR. DONALD E. PICKERING, DR. DELBERT A. FISHER, KENNETH G. SCOTT, PH.D., and DR. FRANCIS SCOTT SMYTH, San Francisco.

Quantitative aspects of iodine metabolism are reported as one among a series of correlated studies regarding general growth and metabolism in normal and athyroid infant macaque monkeys. Methods included use of I^{131}, butyl-extractable iodine determinations, and application of principles of isotopic dilution. In addition, a method for the biosynthesis of I^{131}-tagged thyroxine is presented.

Data are presented describing certain quantitative aspects of I^{131}thyroid uptake as found in normal animals and as influenced by circulating thyroxine and thyrotropic hormone.

The fate of circulating thyroxine in normal and athyroid animals is discussed. Investigations conducted over a prolonged period following the intravenous injection of tracer quantities of I^{131}-tagged thyroxine into normal and/or athyroid animals described the rate of biological decay and volume of distribution of thyroxine.

Series of butyl-extractable iodine determinations following (*a*) the single administration of a large quantity of *l*-thyroxine into normal and/or athyroid animals and (*b*) cessation of prolonged replacement therapy with *l*-thyroxine in athyroid animals was used to reveal the biological half-life of *l*-thyroxine.

The relationship of dosages of *l*-thyroxine required in athroid animals to (*a*) maintain normal serum butyl-extractable iodine levels and (*b*) alter metabolic, growth, and physical features of athyrosis are presented.

Some Observations on the Biology of Acute Leukemia in Children. DR. JAMES P. KING, DR. RUTH APPLETON, DR. SIDNEY FARBER, AND DR. VIRGINIA DOWNING, Boston.

During the six-year period beginning Nov. 1, 1947, more than 350 children with acute leukemia were observed by the tumor therapy group in the Children's Cancer Research Foundation and the Children's Hospital in Boston.

This paper deals with an analysis of some of the variations in history, clinical findings, bone marrow, hematological findings, morphology, and survival time, with reference to response to various forms of therapy.

A summary of these observations with illustrative examples will be presented.

The Persistence of Group A Streptococci in the Tissues of the Rabbit. Dr. Floyd W. Denny Jr. and Dr. Lewis Thomas, Minneapolis.

Group A streptococcal infections of the throat in man are symptomatically of short duration, but the host in a high percentage of cases continues to harbor the infecting organism in the tonsils or pharynx for a period of weeks or months. In view of the capacity of this organism to persist for long periods in the tissues of man, it seemed of interest to determine its capacity to persist in the tissues of the rabbit.

When large numbers of Group A streptococci are injected intravenously into rabbits, cultures of the blood are usually positive for 2 or 3 days and become negative after periods of 7 to 10 days. Two types of experiments were designed to determine the fate of these organisms.

In the first set of experiments, rabbits were killed and their hearts, livers, spleens, and kidneys cultured at various intervals after infection. It was found that the infecting strain of Streptococcus could be isolated from one or more of these organs after the disappearance from the blood stream in approximately 25% of cases. In some animals, streptococci were found in organs 35 days after infection.

In the second set of experiments animals were treated with cortisone after intervals of six weeks and three and one-half months following infection and blood cultures were taken each day during treatment. In approximately 50% of these animals, Group A streptococci reappeared in the blood during the period of cortisone treatment.

These data indicate that the Group A Streptococcus can persist in the organs of the rabbit, without blood-stream dissemination, for long periods of time.

Recent Studies on the Growth of the Mandible in Newborns and Their Clinical Implications in the Management of Micrognathia. Dr. Julius B. Richmond and Dr. Samuel Pruzansky, Chicago.

The development of accurate techniques for infant cephalometric roentgenography during the past four years has made possible long-term longitudinal studies of infants with various growth problems. The largest sample in a collection of records of more than 350 persons consists of newborn infants with a cleft lip and palate. Of this population, a considerable percentage includes infants with micrognathia. Since the attendant glossoptosis and respiratory difficulties are definitely related to the micrognathia, it was of special interest to focus our attention upon the growth of the mandible in such cases.

In reviewing the considerable literature, it appeared that two questions, critical to the management of these cases, remained unanswered. The first question could be phrased as follows: Assuming that the child could be placed in an adequate metabolic climate, how soon would mandibular growth be sufficient to accommodate the tongue and hence insure a more adequate airway? This was the acute problem. The second question related to the long-term prognosis for continued mandibular growth sufficient to provide an esthetically satisfactory facial profile.

In several instances our study has progressed for as long as three and one-half years. During this period we established with reasonable security the following facts:

1. The lateral oriented cephalometric film is a valuable diagnostic tool in assessing the degree of obstruction of the airway. Furthermore, a definite correlation exists between the severity of the symptoms and the degree of airway obstruction noted in the roentgenograms. On the basis of these findings it is possible to prescribe either conservative management or else tracheotomy in extreme situations.
2. Provided the metabolic needs of these children can be met, mandibular growth during the first six months of life is sufficiently prolific to provide an adequate airway within four to eight weeks.
3. To date, our records indicate that mandibular growth continues to progress so that the severity of the retrognathic profile is gradually reduced.

4. Certain patterns of maxillary growth and proliferation of lymphoid tissue in the epipharynx may account for the persistent snoring evident in some of these cases.

Cerebral Blood Flow and Cerebral Oxygen Consumption in Infants and Children. Dr. Henry W. Baird III, Dr. Joseph M. Garfunkel, and Dr. Joseph Ziegler, Philadelphia.

Cerebral blood flow has been measured by the nitrous oxide method in over 50 mentally retarded infants and children; many of the patients had severe defects of the central nervous system. In addition, cerebral oxygen consumption was measured in 25 of these patients. The ages of the subjects ranged from 2 days to 8 years. Twenty-one were less than 4 years of age and 14 were less than 2 years.

In patients with minimal retardation suffering from hydrocephalus or cerebral palsy, the values for cerebral blood flow and cerebral oxygen consumption were comparable to those found in normal adults. However, the values for cerebral blood flow and cerebral oxygen consumption were markedly diminished in those children with severe mental retardation, with or without grossly demonstrable abnormalities of the central nervous system. Low cerebral blood flow and low cerebral oxygen consumption were observed in two patients with hydranencephalus. No elevation of cerebral blood flow above normal was noted in either of two children studied several years after a carotid-jugular anastomosis; in each of these patients the cerebral oxygen consumption was unusually low.

Under most circumstances cerebral functional activity varies directly with both cerebral blood flow and cerebral oxygen consumption. Their measurement would, therefore, appear to offer a means of evaluating cerebral functional activity in children with neurologic disorders.

Serum Cholinesterase. Dr. Virgil Bleisch and Dr. Harry Schwachman, Boston.

A new, relatively simple, and accurate colorimetric determination for serum cholinesterase developed by Ravin and Seligman made it possible to study cholinesterase activity in a large number of patients. This microprocedure requires 0.1 ml. of serum. Data will be presented to show the results obtained in patients with liver disease, malnutrition, and a variety of disturbances encountered in a large pediatric center. Some correlation will be made between serum cholinesterase and liver function tests as performed by Gellis and Hsia.

Serum Beta-Glucuronidase in Cystic Fibrosis of the Pancreas. Dr. G. E. Gibbs, Baltimore.

In an attempt to find further evidence of a primary disorder of mucin metabolism in cystic fibrosis of the pancreas, serum levels of beta-glucuronidase were determined. The average of the values obtained in cases of the disease was insignificantly higher than in controls.

Normal infants were found to have significantly higher levels than children.

Prophylactic Iron in Infancy. Dr. W. L. Niccum, Dr. Robert L. Jackson, and Dr. Genevieve Stearns, Iowa City.

The desirability of preventing, rather than treating, iron-deficiency anemia in infants is well recognized. Various amounts and types of iron compounds have been advised for this purpose. This study was undertaken to determine the desirability of using iron compounds prophylactically during infancy and the relative effects of ferrous and ferric salts.

Five milligrams of iron as ferric or ferrous iron was added to the milk formulas of full-term, immature, and prematurely born infants at 12 weeks of age and increased to 10 mg. of iron by 27 to 28 weeks of age. These infants were observed on the metabolism ward throughout infancy and received nutritionally adequate diets of known content. Hemoglobin values were obtained at weekly intervals. Results are based on 2,804 hemoglobin determinations made on 115 infants receiving ferric ammonium citrate and 304 hemoglobin determinations made on 18 infants receiving ferrous sulfate. In addition, 53 hemoglobin determinations were made on 19 infants receiving ferrous sulfate who were observed in the well-baby clinic.

The customary fall of hemoglobin values after the 20th week of life did not occur in either the group of infants fed ferrous sulfate or ferric ammonium citrate. The mean hemoglobin

value of the group of infants fed ferrous sulfate was significantly higher at 38 weeks of age than the mean hemoglobin values of the infants fed ferric ammonium citrate (13.1 ± 1.24 gm. per 100 ml. and 11.7 ± 1.15 gm. per 100 ml., respectively). The hemoglobin values recorded for the infants fed ferrous sulfate compare favorably with values reported in the literature when 25 mg. of ferric iron and 1 mg. of copper was added to infants' diets.

The study shows that full-term infants when fed an adequate diet including 5 mg. of ferrous iron daily in the formula from 3 to 6 months of age and 10 mg. daily thereafter are able to maintain hemoglobin values at 12 gm. per 100 ml. or above throughout the last half of infancy. Hemoglobin values of infants with serious or recurrent respiratory infections fell to about 10.5 gm. per 100 ml. but rose to 11.5 gm. during the next three months. Immature and premature infants given the same amounts of iron daily were able to maintain hemoglobin values between 10.2 and 11.5 gm. per 100 ml.

It is concluded that these amounts of ferrous iron permit maintenance of a high normal hemoglobin in a healthy full-term infant. The infant with a serious or with a recurrent febrile illness tends to become anemic, as does the prematurely born infant. The small amounts of iron given in this study have aided materially in prevention of anemia in such infants. The addition of ferrous sulfate to the milk feeding provides iron in a usable form, causes no untoward effects on the gastrointestinal tract of the infant, and is a desirable safeguard against the secondary fall of hemoglobin in the latter half of infancy.

Cerebral Blood Flow and Metabolism in Children Subject to Seizures. Dr. Charles Kennedy, Dr. Louis Sokoloff, and Dr. Philip Duffy, Philadelphia.

The nitrous oxide method for measuring cerebral circulation and metabolism has been adopted for use in children without the need for anesthesia or sedation. Eleven children between the ages of 3 and 14 (mean age, 8.5 years) who were normal mentally and had no abnormal neurological findings were studied. They were receiving no medication at the time of study, and, with the exception of one child who had had a seizure 24 hours prior to the study, all the children had been free of seizures for at least two weeks. The mean values obtained were as follows: cerebral blood flow 90.5 cc. per 100 gm. brain per minute (S. E. ± 5.6), cerebral oxygen consumption 4.70 cc. per 100 gm. brain per minute (S. E. ± 0.24), cerebral vascular resistance 0.93 mm. Hg per cc. per 100 gm. per minute (S. E. ± 0.09). This compares with 54.8 S. E. ± 4.3, 3.34 S. E. ± 0.23, and 1.68 S. E. ± 0.13, respectively, for the same functions in 11 normal healthy young men (mean age, 21.8) who were also studied in this laboratory.

It is concluded that the cerebral blood flow and oxygen consumption are significantly higher, while the cerebral vascular resistance is lower, in the children studied, compared with the values obtained in normal healthy young men.

The Effect of Diets of Varying Calcium-to-Phosphorus Ratio and of Vitamin D on the Serum Citrate Levels in the Newborn During the First Week of Life. Dr. Isaac F. Gittleman, Dr. Joseph B. Pincus, Dr. Emanuel Schmerzler, and Dr. Albert E. Sobel, Brooklyn.

Shorr, Harrison, and others have demonstrated that an intimate relationship exists between citrate and calcium metabolism. We and others have shown that diets of varying calcium and phosphorus composition affect the serum levels of these elements in infants during the first week of life. The high-phosphate diets or diets containing a calcium to phosphorus ratio like the one found in processed milk tend to produce a hyperphosphatemia and hypocalcemia, thus favoring the conditions that may precipitate tetany of the newborn. This tendency we found is aggravated by the addition of vitamin D to the diet.

We therefore studied the effect of diets consisting of processed milk of varying calcium-to-phosphorus ratio and of breast milk with and without vitamin D on the serum citrate, calcium, and phosphorus levels. We found that the citric acid level almost invariably fell from what it was on the first day of life to a level of 15% to 70% of its original value by the end of the experimental period. The fall in the serum citric acid level occurred independently of the rise or fall of either the calcium or phosphorus levels in the blood serum. The presence or absence of vitamin D in the diet had no appreciable influence on the serum citric acid level.

We therefore concluded that the metabolism of calcium and phosphorus during the first week of life seems to be independent of the metabolism of citric acid.

The Influence of Dextran on the Dilution of Plasma and the Excretion of Urine. Dr. John T. Olive Jr., Dr. Jesse L. Bollman, and Dr. Roger L. J. Kennedy, Rochester, Minn.

Some patients with the nephrotic syndrome treated with repeated infusions of dextran will exhibit marked diuresis and a reduction in plasma protein below the level expected from hemodilution and excretion. Investigation of these phenomena was undertaken in dogs.

In normal dogs dextran will produce an increase in blood volume above control levels, and this increase may be maintained for 4 to 10 hours. The height and duration of this increase is proportional to the volume of infusion and the molecular weight of the dextran. The increase of volume of the plasma may exceed the volume of dextran injected. This increment of fluid apparently results from the high osmotic gradient between plasma and interstitial fluid that occurs immediately after dextran is infused.

The hypervolemia apparently brings about an increase in the glomerular filtration rate and urine flow. Clearance of exogenous creatinine was increased 25 to 40% over control levels one to three hours following the infusion of dextran. Urine flow was increased to 8 to 10 times the control level and lasted for several hours.

In dogs given dextran at various dosages there is a short initial rise in the total plasma proteins at 5 to 15 minutes after infusion. This is followed by a gradual reduction below normal, reaching a maximum at three to six hours. Gradually, these levels return to normal at 6 to 12 hours. Albumin seems to be reduced more than the globulin fraction. Studies with radioactive iodinated serum albumin after the infusion of dextran indicate there is a significant increase in the rate of diffusion of albumin from the plasma.

Dogs receiving dextran, 1.6 gm. per kilogram of body weight three times weekly over 63- to 129-day periods show no significant change in plasma proteins, glomerular filtration rate, and general health.

Abstracts from Current Literature

Biochemistry; Bacteriology and Pathology

Nosocomial Infections with Reference to Airborne and Dustborne Bacteria. Gunnar Löfström, Nord. med. **46**:1185 (Aug.) 1951.

Report of a study of air-borne nosocomial infections was made. The author emphasized the importance of isolation rooms in children's hospitals, in which each child is admitted and examined from the bacteriological point of view before being transferred to a general ward. Good hospital discipline, efficient bacteriological service, and adequate chemotherapy against the spread of pathogenic bacteria are essential. Further research should be made into the use of ultraviolet light barriers for isolation cubicles in children's hospitals, maternity wards, and operating rooms. Air disinfection by means of chemicals may be considered in connections with an epidemic or as a measure against bacteriological warfare.

Wallgren, Stockholm, Sweden.

Metabolism; Infant Feeding; Milk and Other Foods

The Effect of Epinephrine and Insulin on the Plasma Potassium Level. Abraham Dury, Endocrinology **49**:663 (Nov.) 1951.

Insulin, epinephrine, and desoxycorticosterone acetate have each been reported as affecting the level of blood potassium.

This paper presents evidence that a significant decrease in the level of plasma potassium was induced with epinephrine, which did not involve the mediation of the adrenal cortex; that insulin's apparent effect on the plasma potassium level in normal intact rats was mediated via the adrenal medulla, and that the blood glucose level, as such, does not have any effect on the level of plasma potassium.

Jacobsen, Buffalo.

A Sex Difference in the Tolerance of Wistar Rats for Potassium. Theodore Robertson, Endocrinology **50**:569 (May) 1952.

Rats of various ages were subjected to a potassium tolerance test which consisted of four intraperitoneal injections of potassium chloride solution given at intervals of two hours. Both intact and adrenalectomized female rats 2½ months old showed a greater tolerance for potassium than did comparable male rats of the same age.

The possibility is briefly discussed that an ovarian secretion in some way enables the young female rats to dispose of the excess potassium in a more efficient manner than can their male counterparts and that this action is independent of adrenocortical secretion.

Jacobsen, Buffalo.

Nutritive Value of Lard as Affected by the Proportion of Fat in the Diet. Ralph Hoagland, G. G. Snider, and C. E. Swift, J. Nutrition **47**:399 (July) 1952.

The authors report that in present experiments with growing rats fed isocaloric diets containing 5.0, 10.98, and 18.27% of lard no statistically significant differences were found in the gains of weight; in the storage of fat, protein, or energy, or in the efficiency of utilization of the energy in the feed consumed.

Fredeen, Kansas City, Mo.

The Amount of Nitrogen Retained by Six Young Women on an Intake of Approximately Seventy Gm. of Protein a Day. Frances A. Johnson and Thelma J. McMillan, J. Nutrition **47**:425 (July) 1952.

The authors report that the retention of 0.64 gm., or approximately 6%, of nitrogen per day on an intake of approximately 70 gm. of protein (11.2 gm. of nitrogen) by the subjects of this

study over a 12-week period is approximately the same as the amount observed by others who have studied young women on similar intakes and consuming self-selected diets presumably similar to ones upon which they have been living for a long period of time.

FREDEEN, Kansas City, Mo.

THE ROLE OF THE RETICULOENDOTHELIAL SYSTEM IN VITAMIN A AND CHOLESTEROL METABOLISM. HAROLD Z. BROWN, IRVING PHILLIPS, and B. M. KAGAN, Metabolism **1**:349 (July) 1952.

The relationship between integrity of the reticuloendothelial system and the response to ingested vitamin A was studied in guinea pigs. Trypan red and thorium dioxide were injected intraperitoneally on three successive days to impair normal function of the reticuloendothelial system, and on the following day vitamin A was given by stomach tube in dosage of 6,000 I. U. per pound of body weight. In the animals which were given injections of substances affecting the reticuloendothelial system, the level of the vitamin in the serum (which was within the normal range prior to ingestion of the test dose) rose to abnormally high levels and usually remained elevated for a period of 24 hours. In control animals the average rise in vitamin A was from 21.9 to 363 γ per 100 cc. in three hours, whereas in the animals with impairment of function of the reticuloendothelial system the corresponding values were 20.5 and 1,287 γ, respectively. Serum cholesterol levels were also increased after the injections, there being no disturbance of the ratio between free cholesterol and its esters. The authors draw attention to previous observations that similar responses to ingested vitamin A were found in patients with the nephrotic syndrome.

KAPLAN, Cincinnati.

ARTIFICIAL FEEDING OF WELL BABIES. M. P. BHAGOT, Indian J. Child Health **1**:491 (Oct.) 1952.

The essentials of infant feeding are well and clearly outlined. Addition of solid foods in the diet is only briefly discussed.

McGUIGAN, Evanston, Ill.

BREAST FEEDING. K. C. CHAUDHURI, Indian J. Pediat. **19**:12 (Jan.) 1952.

The author lists the time-honored arguments in favor of breast feeding. Very brief mention is made of techniques, quantity of feeding, psychological aspects, and social aspects. The article is too brief to be of value other than as a reminder.

McGUIGAN, Evanston, Ill.

A PECULIAR OCULAR MANIFESTATION OF ARIBOFLAVINOSIS. D. PAL, Indian J. Pediat. **19**:115 (July) 1952.

Seven patients with ariboflavinosis out of 300 showed a peculiar magenta red discoloration of the palpebral conjunctiva. The color was identical with the color of the glossitis present with ariboflavinosis and was present along with other typical signs of this deficiency.

McGUIGAN, Evanston, Ill.

DIFFERENTIAL CAPILLARY-VENOUS GLYCEMIA FOLLOWING DEFICIENCY OF GLUCOSE AND GALACTOSE IN THE BABY IN NORMAL AND PATHOLOGICAL CONDITIONS. M. ORSINI and L. CAMPEA, Arch. ital. pediat. e puericolt. **14**:285, 1951.

Orsini and Campea state that in the regulation of alimentary hyperglycemia a main part is due to interstitial storage of the excess circulating glucose, which is represented by the increase of capillary-venous differential glycemia. They then report the findings obtained from a series of investigations carried out on 20 children: 10 normal, 7 with hepatic dysfunctions, and 3 with troubles of glucose metabolism (2 diabetic and 1 with glycogenic disease). In each case the behavior of differential glycemia was studied and compared after glucose and galactose loading.

At the end of their investigations the authors summarized their findings as follows:

1. In normal persons a load of galactose produces a marked differential glycemia (average values at the top of curves, 28 mg. per 100 cc.; average increase in respect to basal rate, 18.4 mg. per 100 cc., which is a little less than differential glycemia observed after glucose loading, the latter having a greater hyperglycemia-producing effect than galactose.

2. In persons with hepatic dysfunctions, after both glucose and galactose loading, a differential glycemia appears; the amount and behavior is not far from that of normal persons.

3. Cases of diabetes mellitus, as well as of glycogenic disease, are characterized by lack of differential glycemia after glucose loading, which in diabetes often has negative values; whereas galactose with less glycemia-producing effects causes a positive differential glycemia which sometimes (11 cases of diabetes) can reach values that are remarkably higher than in normal persons.

On the basis of these findings, the authors assume that galactose can be, like glucose, metabolized by peripheral tissues both in normal and in hepatic patients. This brings undervaluation of Bauer's, as well as of Fiessinger's, hepatic functional tests, based on the hypotheses that galactose is fixed exclusively or almost exclusively by liver.

The particular behavior noted in two diabetic patients and in the case of glycogenic disease may be attributed to the fact that in these diseases galactose is better tolerated than glucose; its utilization seems to be improved by it. This is indicated in the researches carried out by one of the authors and reported in the study which show a marked anti- and hypoglycemic action of galactose, as well as a marked sparing effect of insulin requirement, produced by a prolonged administration of lactose.

FROM THE AUTHORS' SUMMARY.

STARCH INTOLERANCE. C. VAZQUEZ GONZALEZ, Acta. pediat. españ. **10**:516 (July) 1952.

In a study of 83 children with chronic noninfectious diarrhea and dyspepsia, the author found nine cases of starch intolerance. Complete studies of the amylase, trypsin, and lipases were made with values in each child and according to the group classification of the dyspepsia.

Blood studies in the groups were made according to the following classifications: simple chronic dyspepsia, starch intolerance, and celiac disease. Development charts were also kept according to this classification, as were stool examinations for the amounts of starch granules versus fats and fatty acids.

The diagnostic differences are explained, and full protocols, as well as photographs of children, are included.

Starch intolerance is an illness characterized by repeated diarrhea, produced by the ingestion of starch, in which the complete starch molecules are recovered unchanged in the feces. There is a low level of duodenal amylase found in these children. The defect appears in the first year of life and, if not treated properly, leads to the development of the celiac syndrome. In the celiac syndrome the amylase found in the duodenum is normal in amount.

The diagnosis may be difficult between starch intolerance and celiac disease, but the former occurs in the first year of life; the celiac syndrome appears between the first and second year. The amount of fat and fatty acids in the celiac syndrome is large and consistently present in the feces; whereas in the starch intolerance cases this is not found.

ALLEN, San Francisco.

THE USE OF AMINO ACIDS IN PEDIATRICS. ANGEL BALLABRIGA, Arch. pediat. **1**:13 (July) 1950.

Ballabriga presents a detailed discussion of the amino acids—their chemistry, uses in metabolism, diseases in which they are useful, products available, dosage, methods of administration—and draws the following conclusions:

1. Amino acids should be used when there is hypoproteinemia from whatever cause. The cause may be lack of ingestion of sufficient protein food, failure to absorb protein, failure to utilize protein, or destruction and elimination of proteins, as in hemorrhage.

2. Use of amino acids is especially indicated in premature infants, for poor nutrition in larger children, in protein deficiency diseases, after severe infectious diseases, when there is loss of protein due to pyloric or esophogeal stenosis, in celiac disease, in cystic fibrosis of the pancreas, and in surgical procedures when protein may not be properly utilized.

3. In nutritional anemias the amino acids may be a useful adjunct to treatment.

4. The use of amino acids in nephrosis and in nutritional diseases is for the sole purpose of maintaining a positive nitrogen balance and should not be construed as affecting the course of the disease.

6. Amino acids are well tolerated by mouth, especially in the form of hydrolysates. There are no reactions or contraindications.

7. The dose by mouth is 2 to 3 gm. per kilogram of body weight in infants and 1 to 2 gm. per kilogram in older children.

8. Parenteral and subcutaneous administration require careful precautions to prevent contamination of solutions and disagreeable reactions. Subcutaneous administration is very effective if dehydration does not exist at the time of administration.

The bibliography is quite extensive.

ALLEN, San Francisco.

BLOOD SUGAR LEVEL IN CHILDHOOD. J. B. MAYER, Ztschr. Kinderh. **69**:232 1951.

The blood sugar levels of 700 children aged from 2 to 15 years are presented in table form and show no significant differences in girls and boys and a gradual, but not linear, increase from average values of 77 mg. per 100 cc. at 2 years of age to 92 mg. per 100 cc. at 15 years. No differences of values in over- and underweight children were found; however, the average blood sugar levels showed higher values during periods of increased growth in length and lower values during periods of increased weight growth. Particularly low values are reported in infants; the explanation may be found in the relatively higher number of Langerhans' islands in the fetus and infant than in the older child or the adult.

GLASER, Jerusalem.

FAT ABSORPTION STUDIES IN CHILDREN. LARS SÖDERHJELM, Acta pædiat. **41**:207 (May) 1952.

A total of 98 fat-balance studies, varying from three to seven days' duration, was made on 32 premature infants weighing at the beginning of the studies from 960 to 2,220 gm. The fat content of the diet varies from 2.6 to 7.8 gm. per kilogram per day and was supplied from breast milk (raw, frozen, or heated at various temperatures for different intervals of time) or from cow's milk (pasteurized or subject to heating at various temperatures for different periods). It is concluded that premature infants retain breast-milk fat to a remarkably high degree, even though the breast milk has been frozen or subjected to various heat treatments. Premature infants do not retain fat from cow's milk as efficiently as they do human milk fat. The nature of the heat treatment of cow's milk did not influence the degree of retention.

FROM THE AUTHOR'S SUMMARY.

FAT ABSORPTION STUDIES IN CHILDREN: II. INFLUENCE OF PROPYLENE GLYCOL, LECITHIN, CHOLINE, AUREOMYCIN, AND LOW FAT DIET ON FAT RETENTION IN CHILDREN. LARS SÖDERHJELM, Acta pædiat. **41**:316 (July) 1952.

In a previous study designed to ascertain the effect of the treatment of milk on the efficiency of fat retention in premature infants, it was found that the type of heat treatment of cow's milk or breast milk did not influence fat absorption. On the other hand, when these premature infants were maintained on breast milk, the amount of fat retained was greater than when on cow's milk. In part, one may explain the superior retention of fat in premature infants fed breast milk to differences in unsaturated fatty acid and mineral contents of cow's milk and breast milk (Holt, 1935). Nevertheless, there may be factors other than the types of milk which influence fat absorption.

No differences in fat retention were observed after the administration of propylene glycol, as used in polyvitamin preparation; lecithin; choline, or chlortetracycline (aureomycin). Even with low-fat diets there is a positive retention, indicating little, if any, endogenous fat excretion in the stools. Only in disorders associated with steatorrhea was the fat balance negative when the patients were on a low fat diet.

FROM THE AUTHOR'S SUMMARY.

FAT ABSORPTION STUDIES IN CHILDREN: III. FAT TOLERANCE TESTS. LARS SÖDERHJELM, Acta pædiat. **41**:325 (July) 1952.

A short review is given on the methods used in fat tolerance tests in children. The determination of the total fat in serum according to the turbidimetric method of Kunkel and Ahrens is very simple and may be used as a screening test when poor fat absorption is suspected.

FROM THE AUTHOR'S SUMMARY.

Dystrophy in Infancy and Its Effects on the Child's Later Development. Helge B. Granrud, Acta pædiat. **41**:510 (Nov.) 1952.

Of 53 children with dystrophy of a temporary nature in the first year of life, 50 were followed up and examined at the ages of 11 to 13 years. The dystrophy seems more serious when it occurs in the first 3 months of life, but, once the child is better, he seems to recover more quickly than those who become ill between the 6th and 12th month. There were no demonstrable after effects on either the somatic development or the development of the teeth. One child had a low intelligence quotient, but it could not be considered due to his illness.

From the Author's Summary.

Vitamins; Avitaminoses

Vitamin D Resistant Rickets (Refractory Rickets). John F. Holt, Am. J. Roentgenol. **64**:590 (Oct.) 1950.

The author reviews many characteristics of vitamin D-resistant rickets. The onset occurs early in the postinfantile period and persists into later childhood. The blood chemistry is almost identical to that found in infantile rickets. There is increased fecal excretion of calcium and phosphate due to decreased intestinal absorption of these substances, even in the presence of what would ordinarily be ample amounts of vitamin D. Roentgenographically, the appearance is similar to infantile rickets; however, the changes are likely to be more profound and in unusual locations. Other diseases to be differentiated from vitamin D refractory rickets are chondrodystrophy; osteogenesis imperfecta; hyperparathyroidism; renal rickets; de Toni-Franconi syndrome; late privational rickets; rickets found in certain types of pancreatic, hepatic, or intestinal insufficiency and in congenital biliary atresia. To effect a cure and prevent recurrence, larger doses of vitamin D are necessary. Six cases are reported.

Harrison, Oak Park, Ill.

Vitamin A Poisoning. John Caffey, Am. J. Roentgenol. **67**:818 (May) 1952.

Since 1944, when the first case of vitamin A poisoning was reported, 22 cases have been recorded, all from the Unites States. The early clinical findings are not distinctive. In all cases, six months have elapsed between the beginning of excessive intake and the appearance of swellings in the extremities, which has occurred prior to the 12th month of life in all but one patient. In every patient some of the tubular bones have shown cortical thickening, particularly of the ulnas and metatarsals. Vitamin A concentrates are probably superfluous and potentially toxic preparations, which should not be placed in the hands of mothers for daily feeding to healthy children.

Hodgson, Rochester, Minn.

The Influence of Age, Strain, Castration and Estrogens upon Hepatic Stores of Vitamin A in the Mouse. Benjamin Rush and B. L. Truscott, Endocrinology **49**:461 (Oct.) 1951.

Abundant evidence supports the presence of vitamin A-estrogen associations in the reproductive system. Vitamin A-deficient rats show a persistent cornification of the vaginal epithelium which resembles the vaginal epithelium of rats during estrus. Daily administration of large doses of carotene to female rats results in the continuous presence of a diestrous vaginal smear.

In the experiments reported it was found that the vitamin A content of the livers of normal mice increased with age. The vitamin A content of the livers of castrated mice increased with age, this increase being more marked than that found in normal mice. The increased concentration of vitamin A in the livers of castrated mice was unaffected by sex, gain or loss of weight, or by the addition of subcutaneously placed pellets of estrone.

Jacobsen, Buffalo.

A Study of the Discrepancy in the Thiamine Content of Meat as Measured by the Thiochrome and Rat Growth Methods. O. B. Fardig, N. B. Guerrant, and R. A. Dutcher, J. Nutrition **44**:29 (May) 1951.

Fardig and co-workers found that the growth-stimulating activity of chopped ham, when fed to thiamine-deficient rats, was due to two different factors. The more important of these factors is free thiamine or thiamine in a form readily liberated by the usual extraction or analytical

procedure. The other factor present in the ham which stimulates growth in the thiamine-deficient rat exhibits properties different from those of the free vitamin. This latter factor is heat-stable, is not inactivated by sulfite, is not absorbed on Decalso, and does not fluoresce under conditions in which thiamine is oxidized to the fluorescent thiochrome. It is not definitely known whether this second growth-stimulating factor is in the ham per se or whether it is elaborated by the intestinal flora of the test animal as the result of ingesting the meat supplement, although a relationship with intestinal micro-organism activity is definitely suggested by the reduced apparent thiamine activity of ham when the basal diet contains phythalylsulfathiazole. While the presence in ham of a factor other than thiamine which stimulates growth in thiamine-deficient rats is suggested the possible synthesis of thiamine or some other growth-stimulating factor in the intestines of the thiamine-deficient rat must also be considered. FREDEEN, Kansas City, Mo.

DAILY DETERMINATION OF PLASMA, SERUM AND WHITE CELL-PLATELET ASCORBIC ACID IN RELATIONSHIP TO THE EXCRETION OF ASCORBIC AND HOMOGENTISIC ACIDS BY ADULTS MAINTAINED ON A CONTROLLED DIET. BESSIE L. DAVEY, MEL-LING WU, and CLARA A. STORVICK, J. Nutrition **47**:341 (July) 1952.

The results presented would indicate that a daily intake of 25 mg. of ascorbic acid is not enough for an adult woman to maintain plasma or serum ascorbic acid at a generally accepted "good" level, i. e., 0.6 to 0.8 mg. per 100 ml. A daily intake of 75 mg. of ascorbic acid maintained levels of 0.84 mg. of total ascorbic acid per 100 ml. of serum, 0.73 mg. of reduced ascorbic acid per 100 ml. of serum, 0.66 mg. of total ascorbic acid per 100 ml. of plasma, and 0.61 mg. of reduced ascorbic acid per 100 ml. of plasma. White cell-platelet levels averaged 21.3 mg. per 100 ml. It is suggested that these levels are all "good."

There is no evidence from this study to indicate that there was any disturbance in tyrosine or phenylalanine metabolism as a result of the lowered ascorbic acid intake. Urinary excretion of homogentisic acid was increased in none of the subjects studied.

FREDEEN, Kansas City, Mo.

VITAMIN B_{12} AND FOLIC ACID IN MILK DIETS. R. A. COLLINS, M. SCHREIBER, C. A. ELVEHJEM, and E. B. HART, J. Nutrition **49**:485 (March) 1953.

Collins and his associates found that the inferior growth of rats fed a mineralized goat's milk diet was the result of a vitamin B_{12} deficiency. Rat growth equal to that obtained with a cow's milk diet was attained when 0.5γ of vitamin B_{12} was added per rat per day to a goat's milk diet or when 3γ of vitamin B_{12} was added per liter of goat's milk. The extent to which folic acid spares vitamin B_{12} may depend upon the vitamin B_{12} stores of the animals. Folic acid and vitamin B_{12} additions to mineralized goat's milk or cow's milk diets did not influence the rate of hemoglobin formation in the normal or anemic rat. Since no clinical evidence is available, it is not possible at this time to estimate the extent to which the low vitamin B_{12} content of goat's milk may contribute to "goat's milk anemia" in infants. FREDEEN, Kansas City, Mo.

THE EFFECTS OF VITAMINS B_{12} AND B_{12r} ON GROWTH, KIDNEY HEMORRHAGE, AND LIVER FAT IN RATS FED PURIFIED DIETS. EDGAR A. HAWK and C. A. ELVEHJEM, J. Nutrition **49**:495 (March) 1953.

Hawk and Elvehjem conclude that there is no doubt that vitamin B_{12} spares choline, but the degree of sparing depends upon the criterion used for choline deficiency. When judged only on the basis of growth stimulation or kidney protection, dietary choline may not be needed when an adequate amount of vitamin B_{12} is supplied. When the criterion is the level of liver fat, the lipotropic action of vitamin B_{12} can be demonstrated only in the presence of suboptimum dietary choline. It is of interest to note that vitamin B_{12} may actually increase the level of liver fat, possibly by promoting the synthesis of enough choline to satisfy the requirement for growth but not enough to promote the movement of fat out of the liver. No evidence was obtained of a choline-sparing activity of vitamin B_{12r}. Methionine will not replace choline completely, even in the presence of supplementary vitamin B_{12}.

FREDEEN, Kansas City, Mo.

STORAGE AND ELIMINATION OF VITAMINS B_{12} IN THE RAT. ROBERT A. HARTE, BACON F. CHOW, and LOIS BARROWS, J. Nutrition **49**:669 (April) 1953.

The authors present data on the storage of radioactivity in selected target organs following administration to rats of Co^{60} containing vitamin B_{12}. These experiments point out that significant and prolonged storage, up to three months, occurs in the pancreas of the rat. The effects on storage in selected organs of flooding of the host with the vitamin have been studied. Some evidence suggestive of flushing out in liver and pancreas has been found, but the storage of radioactivity in the kidney appears to be unaffected. The state of saturation of the host has been shown to play a role in the extent of storage of a tagged dose in the liver, pancreas, and kidneys. In the liver and pancreas, storage is less in the saturated animal, while greater storage is seen in the kidneys. The data on persistence of storage as determined in the rat may possibly offer a satisfactory explanation for the relatively prolonged therapeutic effect of B_{12} injections in pernicious anemia in man. The data presented in this report are not to be interpreted as quantitative, since no attempts were made to introduce all of the refinements requisite for the most precise determinations of radioactivity. The authors suggest that their broad conclusions are properly to be regarded as guideposts to future programs of study.

FREDEEN, Kansas City, Mo.

THE RELATION OF THYROID ACTIVITY TO METABOLISM OF NICOTINIC ACID. R. CORDA, Ann. ital. pediat. **5**:486 (Dec.) 1952.

The author has studied the utilization of nicotinic acid in the animal organism in relation to thyroid action, verifying its hematic quantity before and after vitaminic change in the two opposite conditions of extirpation of the thyroid gland and of experimental hyperthyroidism.

According to his experiences it would seem evident that, while in the increase of metabolic processes greater need of nicotinic acid corresponds to an excessive thyroid activity, in the opposite conditions there may be seen a lack of utilization.

FROM THE AUTHOR'S SUMMARY.

DETERMINATION OF NICOTINIC ACID AND TRIGONELLINE IN THE URINE WITH DEFICENCY OF NICOTINIC ACID. G. NICHELE, Arch. ital. pediat. e puericolt. **15**:77, 1951

The urinary excretion of nicotinic acid and of trigonelline was investigated in 15 persons after administration of 100 mg. of nicotinic amide. It was found that this drug was eliminated in quantities of nicotinic acid from 0.06 to 2.77 mg. per cc. and from 1.86 to 21.81 mg. per 100 cc. as trigonelline. The author thinks that the greatest part of the nicotinic amide administered is transformed in the body into trigonelline and then eliminated in urine under this form.

FROM THE AUTHOR'S SUMMARY.

THE ELIMINATION IN THE URINE OF NICOTINIC ACID, NICOTINURIC ACID AND OF TRIGONELLINE IN TESTS FOR DEFICIENCY OF NICOTINIC ACID AND ITS AMIDES. GILDO NICHELE and VITTORIANO BOCCARDELLI, Arch. ital. pediat. e puericolt. **15**:99, 1951.

The urinary elimination of nicotinic acid and its derivatives (trigonelline, nicotinuric acid) in 10 children before and after administration of sodium nicotinate and in 5 children after administration of nicotinamide was studied. The two substances caused an increase of urinary elmination of nicotinic acid and trigonelline and the appearance if nicotinuric acid in the urine.

The sodium nicotinate (30 mg.) was eliminated as nicotinic acid, with values from 3.66 to 27.20%; as trigonelline, with values from 1.37 to 35.53% and as nicotinuric acid, with values from 10.8 to 27.50%. The nicotinamide (100 mg.) was eliminated as nicotinic acid, with values from 1.42 to 3.52%; as trigonelline, with values from 6.72 to 20.40%, and as nicotinuric acid, with values from 0.49 to 1.70%.

Nicotinuric acid appeared in urine only after parenteral introduction with nicotinic acid; higher excretion with sodium nicotinate than with nicotinic amide was noted.

FROM THE AUTHORS' SUMMARY.

VITAMIN T (GOETSCH) IN DYSTROPHIC AND ATROPHIC INFANTS. B. ANGELINI and E. PENNATI, Minerva pediat. **4**:1066 (Dec. 31) 1952.

Vitamin T (Goetsch) is not a true vitamin but is an extract of torulae, which are part of the food of the fast-growing giant termite larvae; this extract is a mixture of substances, the active ingredient, or biocatalyzer, being not yet established. The efficacy of this extract was tested on 16 dystrophic and 2 premature infants, with promising results, as indicated by gains in weight and in blood hemoglobin and cholesterol. Further discussion of vitamin T is contained in a review on nutrition by the same authors on page 1082 of the same issue of *Minerva pediatrica*.

HIGGINS, Boston.

ETIOPATHOGENIC PECULIARITIES OF RACHITIS IN SPANISH CHILDREN. B. TARACENA DEL PIÑAL and J. MATOS AGUILAR, Acta pediat. españ. **10**:155 (Feb.) 1952.

The author gives a very full but quite concise history of the discovery of the etiology and pathological findings in rickets. The author studied children and their histories, as recorded in dispensaries in three different groups. One hundred children from fairly comfortable privileged families living in large cities were treated by family physicians; 1,000 children living in large cities were seen in dispensaries, and another thousand were from definitely backward rural areas. X-rays; diet; serum calcium, phosphorus, and phosphotase determinations were made, as well as the study of clinical findings in these children. The children's ages ranged up to 5 years.

The author provides many illustrations and the protocol of representative numbers of cases in each group. Included also is the study with the amount of sun in all parts of Spain at various times of the year.

His conclusions were as follows:

1. Few of the children had any other chronic disease, such as syphilis or tuberculosis.

2. The children of the higher economic classes had the fewest cases of rickets, although they lived in large cities.

3. In children living in the country in one of the poorest rural areas, the per cent of children having rickets was 11.7%.

4. In the city, where the poorer people have access to the clinic, the per cent of rachitic children is 12.6%.

5. Breast feeding or artificial feeding plays very little part in the incidence of these cases.

6. In the cases studied the blood studies showed normal values for calcium, phosphorus, and alkaline and acid phosphatases.

7. Psychic, somatic, and radiographic development was retarded in at least 50% of these children.

8. The diet in all instances was frankly quite low in vitamin B and protein, and the protein-plasma studies showed a lower figure in all cases than the protein values found in normal children of the same age.

9. The deficit of vitamins A and D does not seem to have too great a bearing on these cases.

10. Children who display clinical signs of rickets in Spain have at least severe nutritional deficits in protein and vitamin B.

ALLEN, San Francisco.

TWO OTHER CASES OF ACUTE HYDROCEPHALY FROM MASSIVE DOSES OF VITAMIN A. PEDRO GONZÁLEZ OUTÓN, Acta pediat españ. **11**:122 (Jan.) 1953.

Outón reports two cases of children who took massive doses of vitamin A and acute hydrocephaly developed. The author says the product used was hydrosoluble and he had used it with numerous children without ill effects. The children who did not have hydrocephaly were not given massive doses but received usual doses over a period of time.

One child maintained a tense fontanel for three months after the vitamin product was stopped. Both eventually recovered.

One child had a family history which was significant for the large number of allergic manifestations, although the child herself had none of these symptoms.

ALLEN, San Francisco.

THE EFFECT OF VITAMIN B_{12} IN MALNOURISHED INFANTS. M. B. DEMEZEI, Arch. argent. pediat. **37**:31, 1952.

A brief review of the pertinent literature is made plus observations in seven controls and in eight patients treated by the author. She concludes that vitamin B_{12} appears to have beneficial effects on weight gain in malnourished infants.

PANOS, Galveston, Texas.

RACHITIS PROPHYLAXIS. O. HOVELS, Med. Klin. **47**:1631 (Dec. 5) 1952.

The prevalence of florid rickets in certain Hessian districts could be traced to faulty feeding. It was noted that the increased frequency of rachitis after the second month of life was due to feeding of mixtures of milk and oatmeal decoctions in equal amounts. With milk mixtures containing two-thirds milk or with whole milk, the frequency of rachitis decreased. The special injurious effect of oatmeal decoctions is seen in the fact that oatmeal is rich in phytinic acid, which combines with the calcium of food, preventing its resorption. The proper prophylactic use of Vigantol (irradiated ergosterol preparation) is discussed with regard to dosage and time of medication.

AMBERG, Rochester, Minn.

PRENATAL PROPHYLAXIS OF CONGENITAL INFANTILE RICKETS. S. LIEBE, Montasschr. Kinderh. **100**:41 (Feb.) 1952.

Of 305 newborn infants born to mothers who had received no antirachitic treatment during pregnancy, 169, or 54.4%, were found to have rachitic ossification disturbances of the distal ulnar and radial epiphyses. Of 238 newborn infants of mothers who had received one oral dose of 15 mg. of calciferol (vitamin D_2) about eight weeks prior to delivery, only 78, or 32.8% showed these rachitic bone changes. Thus it was shown that prenatal prophylaxis with calciferol could reduce the occurrence of congenital rickets but could not prevent it completely.

No direct relationship was established between such maternal findings as toothaches, loosening of teeth, dental caries, bone pain, easy fatigability, hyperhidrosis, and alopecia, all usually thought to be typical of puerperal osteomalacia, and the occurrence of congenital rickets in infants born to such mothers. Therefore, the author concludes that such maternal signs and symptoms should no longer be considered pathognomonic of puerperal osteomalacia.

HARTENSTEIN, Medical Corps, United States Army.

Hygiene; Growth and Nutrition; Public Health

CHEMICAL GROWTH IN INFANCY AND CHILDHOOD. GILBERT B. FORBES, J. Pediat. **41**:202 (Aug.) 1952.

Infancy and childhood is a period of chemical as well as physical and emotional maturation. In this comprehensive review, Forbes points out the gaps in our present-day knowledge of chemical growth.

MACDONALD, Pittsburgh.

GROWTH OF NORMAL INFANTS. L. M. SUKTHANKAR, Indian J. Child Health **1**:175 (April) 1952.

The author studied the growth pattern of 240 normal Hindu infants by measuring weight, height, and head sizes. He presents charts showing average growth curves which can be used as a basis of comparison in individual infants. He concludes that the rate of growth is greater in boys than in girls and greater for small babies than for large ones. Rate of weight increase tends to be the same for all babies of the same sex during the first year. Increase in head size is nearly the same in both sexes; whereas increase in height is slightly greater in boys.

MCGUIGAN, Evanston, Ill.

CHILD WELFARE IN THE FAR EASTERN REGIONS. J. F. BULSARA, Indian J. Child Health **1**:539 (Nov.) 1952.

The high infant mortality in the far eastern sections of India is discussed, with consideration of etiologic factors. Measures to improve this situation are reviewed, and needs for further work are pointed out.

MCGUIGAN, Evanston, Ill.

CHILD WELFARE SERVICE IN WEST BENGAL. C. DAS GUPTA, Indian J. Child Health **1**:546 (Nov.) 1952.

Organization of child welfare services in West Bengal is discussed, this being a function of the government. The scope and extent of the services is outlined, as applies to maternal and infant care programs which are established and operating effectively. One health center is provided for every 10,000 population. Training courses are provided to train personnel to maintain these services. School health services are widespread and effective. In large measure these provide care for the older child, as the other programs do for the infant.

McGUIGAN, Evanston, Ill.

HEALTH WORK IN BOMBAY MUNICIPAL SCHOOLS. V. R. B. BHOOSRATH, Indian J. Child Health **1**:585 (Nov.) 1952.

The importance of adequate school health service is stressed. In order to produce healthy adults, children must be freed from health-impeding defects. The author cites five health agencies existing in the public schools: school hygiene, meaning environmental hygiene; personal hygiene, a phase of health education; physical education; medical inspection of children, and school medical relief, involving free clinics and first aid services. Expansion of all these aspects of school health is badly needed.

McGUIGAN, Evanston, Ill.

PHYSIOLOGICAL "NORMS" IN INDIANS: I. GROWTH CURVES OF CHILDREN IN FIRST MONTH. M. N. RAS and B. BHATTACHARJEE, Indian J. Pediat. **19**:1 (Jan.) 1952.

The authors endeavored to establish a "normal" growth curve for Indian children, since normal growth patterns are not available for this race. Forty-six normal full-term babies were studied, and their growth over the first month was plotted. The average baby was found to weigh 6.5 lb. (3.0 kg.) at birth, to lose 9 or 10 oz. (340.19 gm.) in the first 3 days and to regain its birth weight in the next week. Subsequent weight gain averaged 1.1 to 1.3 oz. (31.2 gm.) daily.

McGUIGAN, Evanston, Ill.

CHILD HEALTH WORK IN INDIA. S. K. ROY, Indian J. Pediat. **19**:57 (April) 1952.

The various aspects of child health work in India are briefly reviewed. The author points out the lack of facilities and personnel and the severe nutritional and financial limitations which affect the majority of the population. Every branch of child welfare is deficient, and improvement in both education and legislation to help provide services is needed.

McGUIGAN, Evanston, Ill.

NUTRITION AND HEALTH STUDY ON BANTU BOYS. HARDING LE RICHE, A. A. KINNEAR, L. J. A. LEOWENTHAL, P. H. BOSHOFF, RYNO J. SMIT, South African M. J. **27**:103 (Jan. 31) 1953.

This is the final evaluation and conclusions in a series of papers devoted to an intensive survey of nutrition and health among Bantu boys. Two groups of thirty each were studied, one being placed on a nutritionally adequate diet, and the other on a diet typical to native Bantus. The study extended over a period of 16 months.

At the end of the study, boys on the poorer diet were slightly shorter and lighter than the others, though not significantly so. Comparison of hemoglobin, urine, vitamin deficiencies, dental health, and cardiovascular systems showed no significant differences. There were more cases of ocular infection in the less adequate diet, though these could not be related to vitamin A or C levels.

Illness was not more frequent in the lower group, but such illness as occurred tended to last longer.

McGUIGAN, Evanston, Ill.

My Experience on the Effects of Treatment in Cases of Retarded Growth. G. Maranon, Acta pediat. españ. **10**:887 (Nov.) 1952.

Dr. Maranon gives the results in the treatment of retarded growth in approximately 2,500 children who have been followed since 1932. Dr. Maranon is aware of the great amount of controversy regarding the possibility of proving that the height of a given child can be increased. Those most convinced of this possibility have reported excellent results from the use of extract from the anterior lobe of the hypophysis, the growth hormone.

The efficacy of treatment depends on the nature of the deficit, familial factors, the duration of the pathology, and the age of the child.

The diagnostic categories and the results after treatment are given. They are transitory retardation in height (no effect with growth hormone); hypophyseal infantilism, inanition (possible help with hypophyseal, thyroid, and gonadal extracts in small doses); primitive thyroid infantilism, inanition (definite improvement on thyroid); infantilism, inanition, cretin (slight results with any or all hormones); primitive ovarian infantilism (slight results with ovarian and thyroid hormone); neurogenic infantilism (no improvement with any treatment); infectious infantilism, inanition (no improvement with hormones); infantilism associated with visceral lesions, cardiopathies mainly (no improvement with hormonal treatment; better results after surgery, etc.); infantilism due to poor nutrition (quick recovery with proper regimen; hormonal treatment later efficacious); constitutional infantilism, inanition (ineffective); hypergenitalism (no response to any treatment); achondroplasia and dyschondroplasias (no response); rachitic inanition (response to vitamins; later surgery); Pott's disease (may improve with general treatment and/or orthopedic surgery).

Prognosis is more favorable in families made up of medium and tall persons. The lack of growth may be a transitory retardation or a mistake in the plotting of the growth curve.

All cases respond more quickly when treatment is started early.

The author outlines the treatment with hormones, vitamins, etc. Amino acids are used, as well as zinc phosphate which has been shown to increase growth in experimental animals. Iron and iodine should be used when indicated.

Allen, San Francisco.

Juridical Aspects of Family Problems and Possible Solutions. Juan B. Carballa, Bol. Inst. internac. am. protec. infancia **23**:263 (Sept.) 1949.

The leading principles of legislation are (1) to determine the extent of transgression that comprises a violation of social interests of family care and of the individual interests of its members; (2) to establish as fully as possible the active and passive participants in the infraction of family relations; (3) to leave prosecution to public action, and (4) to choose, instead of a penalty, the more constructive measures of compulsory work in cases of omission of financial assistance.

All this, within the diverse requirements imposed by the legislation in each country.

From the Author's Summary.

Prematurity and Congenital Deformities

Craniopagus Parietalis: Report of a Case. E. Graeme Robertson, A. M. A. Arch. Neurol. & Psychiat. **70**:189 (Aug.) 1953.

A case of craniopagus parietalis is discussed. An attempt to determine the degree of junction of the twins was followed by immediate deterioration, and the twins eventually died. Detailed anatomical studies are included in the report.

McGuigan, Evanston, Ill.

Clinical and Roentgenological Manifestations of the Klippel-Feil Syndrome. M. I. Shoul and M. Ritvo, Am. J. Roentgenol. **68**:369 (Sept.) 1952.

Shoul and Ritvo discuss the existing literature concerning the Klippel-Feil syndrome and add eight cases to the literature. The Klippel-Feil syndrome is characterized by fusion of two or more of the cervical vertebrae. Feil originally described three types of the condition: (1) that with complete fusion of the cervical portion of the spine, (2) that with partial coalescence of the cervical segments, and (3) that with reduction of the number of cervical vertebrae and fusions and anomalies in other parts of the spinal column.

Clinically, the syndrome is manifested by shortening and limitation of mobility of the neck, lowering of the hair line on the neck, and, in extreme cases, an appearance of implantation of the head on the chest. Confirmation by means of roentgenograms is necessary to establish the diagnosis. In most cases the diagnosis is made by roentgenograms alone, since the external appearance of the patient is not changed enough to suggest the abnormality.

The cause of the abnormality is not known. The authors discuss various embryological theories. In general, the prognosis is good, and the disease is compatible with long life. Frequently other congenital anomalies occur with it and may affect the prognosis. Shoul and Ritvo believe that patients with the Klippel-Feil syndrome are particularly susceptible to fracture of the cervical vertebrae and should take precautions to avoid trauma to the neck. Two of their eight patients sustained fractures, resulting in the sudden death of one.

The Klippel-Feil syndrome may produce neurologic symptoms and signs in some patients. Symptoms suggesting pressure on the cervical portion of the spinal cord and on the cervical nerve roots in patients having short necks should suggest the diagnosis. One of the authors' patients presented weakness of the right arm and leg, hemiatrophy, and other abnormal neurologic findings.

WEILAND, Grove City, Pa. [A. M. A. ARCH. NEUROL. & PSYCHIAT.].

PRENATAL ENVIRONMENT AND CONGENITAL MALFORMATIONS. ROY STODORD, Bull. Tulane M. Fac. **12**:123 (May) 1953.

Environmental factors which may result in malformations are listed under the headings of nutritional, chemical, endocrine, radiation, infectious, and mechanical factors. Relationships between the time of insult and the type of anomaly are considered.

McGUIGAN, Evanston, Ill.

CALCULATION OF A PREMATURE MORTALITY RATE FOR A HOSPITAL. K. K. MATHEN, Indian J. Pediat. **20**:97 (May) 1953.

The author points out the various factors involved in calculating a premature mortality rate. A standard definition of prematurity must be established, and the rates must be corrected for differences in distribution of the weight at birth.

McGUIGAN, Evanston, Ill.

THE ACTION OF DESOXYCORTICOSTERONE IN PREMATURE AND CONGENITALLY DEBILITATED INFANTS. M. BERTOLI, Lattante **23**:265 (May) 1952.

Eighteen newborn infants, weighing 1,400 to 2,500 gm., were given intramuscular injections of desoxycorticosterone acetate (2 mg. per kilogram) daily for six days. The infants reacted by increased alertness and more stable vasomotor and temperature adjustments. None of the babies died, and many were able to suckle their mothers' breasts.

HIGGINS, Boston.

Newborn

FLUSH METHOD FOR BLOOD PRESSURE DETERMINATION IN NEWBORN INFANTS. DAVID GOLDRING and HULDA WOHLTMANN, J. Pediat. **40**:285 (March) 1952.

Goldring and Wohltmann described a visual method for determining systolic blood pressure in infants. A 2.5 cm. cuff is placed around the ankle or wrist in the usual manner, and a piece of rubber sheeting or old rubber glove is wrapped snugly around the foot or hand, starting distally, so that the blood is pressed from the extremity. The cuff is then inflated to a pressure slightly above the suspected systolic pressure. The rubber bandage is then removed from the blanched extremity, and the pressure is reduced in the cuff—not faster than 6 to 7 mm. per second. Blood reentering the foot or hand causes a sudden flush. The approximate systolic pressure is read at this point. From the few studies made, the authors suggest that a difference greater than 20 mm. Hg between the upper and lower extremities suggests a diagnosis of coarctation in a suspected case.

MACDONALD, Pittsburgh.

Congenital Entero-Umbilical Fistula Due to a Patent Vitelline Duct. Howard E. Scalettar, Milton M. Mazursky, and Henry Rascoff, J. Pediat. **40**:310 (March) 1952.

When the Funis clamp was removed from the infant's umbilicus one day after birth, the area around the umbilicus was red and slight pressure extruded meconium through the umbilical opening. The patent vitelline duct, a relatively rare anomaly, was excised. The infant recovered.

Macdonald, Pittsburgh.

Renal Thrombosis Complicating Epidemic Diarrhea of the Newborn: Nephrectomy with Recovery. H. William Clatworthy Jr., Dale R. Dickens, and Charles R. McClave, New England J. Med. **248**:628 (April 9) 1953.

Acute ileocolitis, either as it occurs in epidemic diarrhea of the newborn or as an isolated illness, is frequently complicated by renal thrombosis. This acute occlusive phenomenon involves the renal venous system either partially or totally and results in destruction and loss of function of the parenchyma by hemorrhage. Dehydration and septicemia are almost always contributory factors.

Evidence of renal involvement may be present in the form of hematuria and the existence of a mass in the region of one or both kidneys. Intravenous pyelography is a valuable diagnostic aid as well as the means by which the presence of a remaining functioning kidney, uninvolved in the thrombotic process, may be ascertained.

The treatment is surgical removal of unilaterally infarcted kidney, and good results are common. Surgery is done only after the other kidney is seen to be intact.

Wheelock, Denver, Colo.

Phagocytic and Ameboid Activities of the Leukocytes in the Newborn Infant. Yehuda Matoth, Pediatrics **9**:748 (June) 1952.

Neonatal leucocytes obtained from cord blood were found to have lower ameboid and phagocytic activities as compared with maternal leucocytes and leucocytes of other adults.

From the Author's Summary.

Oximeter Studies in Newborn Infants During Crying. Klara J. Prec and Donald E. Cassels, Pediatrics **9**:756 (June) 1952.

The arterial oxygen saturation was determined in 135 healthy newborn infants during sleep and while crying with a direct-reading single-scale oximeter. In the first group, consisting of infants from 1 hour 30 minutes to 3 days of age, 66% showed a decrease of oxygen saturation with crying, 27% an increase, and 6.8% no change. In the second group, which included all infants between 4 and 9 days of age, 59% showed an increase in saturation with crying, 21% a decrease, and 22.4% no change. In comparison, the mean results in these two groups are in the opposite direction. These changes are statistically significant. Twenty-eight infants were studied also while breathing oxygen (73-98.5%), and the results compared with those in room air showed an identical trend.

It is concluded that increases in arterial oxygen saturation with crying, which occur more frequently in older infants, are probably due to an increase in alveolar oxygen tension secondary to improved pulmonary ventilation during crying.

The paradoxical decrease in saturation during crying, which was found in a large percentage of infants of the younger group, is suggestive of the presence of a transitory venous-arterial shunt. This shunt could be either through atelectatic areas of the lung or through the foramen ovale, which is only functionally closed and can open whenever the pressure in the right auricle exceeds the left auricular pressure. There is some available evidence to support the latter possibility.

From the Author's Summary.

PUBLIC HEALTH ASPECTS OF PROBLEMS OF CURRENT INTEREST IN NEONATAL PEDIATRICS. LEONA BAUMGARTNER, Pediatrics **11**:489 (May) 1953.

The salient facts regarding fetal, neonatal, and infant mortality in the United States are presented, the most recent national figures available or those from other large population groups being used. A plea is made for the use of perinatal mortality rates in order to obtain a better picture of the success of current programs designed to reduce infant loss.

Six areas for future attack are suggested: (1) development of several research institutes to study the problems of human reproduction from a multidiscipline approach; (2) an organized program to raise standards of care in all lying-in hospitals, with particular emphasis on activities which can be carried on by nurses and doctors at the local level; (3) further experimentation with and development of ways to supply better service or pay for medical care for certain groups (more attention could be paid to regional plans whereby services of large medical centers are brought to smaller, less well-cared-for areas; to hospitalizing women with previous history of or current complications of pregnancy, including labor; to providing expert pediatric and obstetric consultation more freely; to supplementing the prenatal diet, etc.); (4) acceleration of activities which bring about closer cooperation between obstetric and pediatric services with full cooperation of general practitioners, nurses, nutritionists, and all those involved in the care of mother and baby, and more local studies of neonatal deaths, with the studies used as the basis for community action and professional education; (5) development of better antepartum service for all mothers in the local community; (6) continued experimentation with methods of solving the many social problems created by the low economic and social status of those families which contribute so heavily to fetal and neonatal mortality rates today.

FROM THE AUTHOR'S SUMMARY.

CLINICAL DIAGNOSIS OF GENERALIZED CYTOMEGALIC INCLUSION DISEASE. ROBERT D. MERCER, SARAH LUSE, and DONALD H. GUYTON, Pediatrics **11**:502 (May) 1953.

A case of generalized cytomegalic inclusion disease is described in which, for the first time, the diagnosis was established during the life of the patient. The clinical syndrome is delineated and the differential diagnosis discussed. It is suggested that the diagnosis of the syndrome can be made clinically in the neonatal period by study of the urine sediment.

FROM THE AUTHORS' SUMMARY.

HÆMATOLOGICAL STUDIES IN NEWBORN INFANTS. BHOLANATH BANERJI, J. Indian M. A. **22**:355 (June) 1953.

Banerji reports that the percentage of hemoglobin, red blood cells, and reticulocytes is higher in the circulating blood at birth than in the cord blood. He makes various suggestions regarding the cause for this, such as splenic contractions, lower oxygen tensions, and higher hematopoietic activity at birth. The red blood cells and hemoglobin both decrease after birth, while reticulocyte percentages increase.

McGUIGAN, Evanston, Ill.

THE BONNEVIE-ULLRICH STATUS IN A NEWBORN INFANT. P. MARUSSI SCARIZZA, Lattante **23**:283 (May) 1952.

Scarizza reports the case of a baby with multiple deformities, who died at the age of 8 days from a congenital malformation of the heart. An unusual scar-like formation was observed over the lambda of the skull; the skin was atrophic; in the corium were multiple microscopic bubbles, similar to those which have previously been described as occurring in the meninges of patients with the Bonnevie-Ullrich status.

HIGGINS, Boston.

Acute Contagious Diseases

POLIOMYELTIS: V. THE PONS. H. A. MATZKE and A. B. BAKER, A.M.A. Arch. Neurol. & Psychiat. **68**:1 (July) 1952.

Detailed histologic studies of the pons in 109 cases of bulbar poliomyelitis showed involvement in almost every case. Degree of histologic damage far exceeded the amount of clinical

dysfunction observed. The authors point out the fact that irritation of the motor nucleus of the fifth nerve may result in difficulty in removal of secretions, requiring tracheotomy. Also, involvement of the part of the vasomotor center located in the pons may produce circulatory collapse and death.

McGUIGAN, Evanston, Ill.

POLIOMYELITIS: VI. THE HYPOTHALAMUS. A. B. BAKER, S. CORNWELL, and I. A. BROWN, A.M.A. Arch. Neurol. & Psychiat. **68**:16 (July) 1952.

Studies of the hypothalamus showed changes in 85% of the cases, with damage to over 5% of the patients in 61% of the cases. It is stated that many patients show clinical evidence of hypothalamic dysfunction, and special tests will show evidence of subclinical changes in the hypothalamus months, or even years, after recovery from bulbar poliomyelitis.

McGUIGAN, Evanston, Ill.

RESPIRATORY FAILURE IN POLIOMYELITIS: A SIMPLE METHOD FOR ITS RECOGNITION AND CONTROL. W. F. STAFFORD JR. and R. GURNEY, Ann. Int. Med. **34**:203 (Jan.) 1951.

The difficulty in recognizing the imminence of respiratory failure and other pulmonary complications in poliomyelitis results in a high mortality rate in this disease. An important contributing factor is failure of the clinician to use the respirator soon enough.

One purpose of this paper is to emphasize an extremely simple method of acquiring objective criteria which are clear-cut indications for use of the respirator. Recognition of impending respiratory failure is readily accomplished by the use of any basal metabolism apparatus capable of measuring vital capacity. With such a machine, a permanent record of the rate and depth of breathing and the maximum possible expiration can be obtained. Swank, by such means, studied the tidal air and vital capacity in five patients with diminished respiratory function, and his findings suggest four stages in the development of respiratory failure: (1) reduction of tidal volume and vital capacity to approximately 350 and 1,000 cc., respectively; (2) the appearance of periodic deep breaths and waxing and waning of the tidal volume; (3) disappearance of the periodic deep breaths; (4) disappearance of waxing and waning of the tidal volume, with further reduction of the tidal volume to approximately 200 cc.

This simple method for the determination of certain aspects of respiratory function which could be used as criteria for the recognition of incipient and advanced respiratory failure seemed especially applicable to patients with poliomyelitis and was utilized by the authors in the cases of five adults with respiratory involvement.

During the test, the patient breathed 100% oxygen in order to prevent hypoxemia. Tracings were made during the early stages of respiratory failure, after total respiratory failure had occurred and the patient was in the respirator, and during the recovery period.

By the use of this method, with repeated respirograms, the authors found it possible to anticipate respiratory failure before it was evident clinically. They emphasize the necessity of measuring vital and minute volumes during artificial respiration. During artificial respiration, pulmonary complications can be demonstrated by this method before any recognizable clinical signs are present. This method also gives a satisfactory indication of return of respiratory function and serves as a guide for evaluation of the patient's ability to withstand removal from the respirator.

ALPERS, Philadelphia. [A. M. A. ARCH. NEUROL. & PSYCHIAT.].

ELECTROPHRENIC RESPIRATION IN ACUTE BULBAR POLIOMYELITIS: ITS USE IN MANAGEMENT OF RESPIRATORY IRREGULARITIES. S. J. SARNOFF, J. V. MALONEY JR., B. G. FERRIS JR., L. C. SARNOFF, and J. L. WHITTENBERGER, J. A. M. A. **143**:1383 (Aug. 19) 1950.

Acute bulbar poliomyelitis is not infrequently complicated by involvement of the center which drives and coordinates respiration.

The difficulties resulting from involvement of the respiratory center are generally thought to be of two types: (*a*) grossly irregular respiratory rhythm and depth and (*b*) lack of coordination of the muscles of respiration.

Attempts to manage the patient with this type of poliomyelitis in the tank type of respirator of Drinker and Shaw are generally thought to be ineffective when involvement of the respir-

atory center is severe. This is largely because of the impossibility of substituting the rhythm of the respirator for the patient's grossly irregular "respiratory fibrillation."

In normal, unanesthetized man, electrophrenic respiration by external stimulation causes prompt suppression of spontaneous respiration, an observation confirmed in over 400 instances. The data cited in this paper support the authors' early hope that in the patient with bulbar poliomyelitis all spontaneous respiration, including the respiratory irregularities, would be suppressed, thus permitting one to supply regular, effective respiration. At least one phrenic nerve must be partially or completely uninvolved if this method is to be employed.

It was found that in nine patients with central respiratory irregularities due to bulbar poliomyelitis the irregularities could be suppressed in each case by electrophrenic respiration and regular effective ventilation provided.

The extraordinary extent and severity of central nervous system derangement that can exist and still be reversible if the critical demands of the respiratory and circulatory systems are met have here been demonstrated by Sarnoff and his colleagues. The electrophrenic respirator is not a hazard in the presence of circulatory inadequacy and may actually elevate the blood pressure and cardiac output in this condition.

The electrophrenic respirator consistently and strikingly diminished the restlessness and hypertension in one patient and achieved similar results in others. The mechanisms involved are not known.

It was thought that nursing care was facilitated in the treated group of patients, as compared with that of the usual tank-enclosed patient.

It is not unlikely that the tank respirator, although it may not succeed in achieving control of respiration, may be able to maintain control of respiration once it has been established. One eventual application of electrophrenic respiration may be to adapt the refractory patient to the tank respirator, should it become desirable to do so.

The usefulness of the electrophrenic respirator cannot be considered as established in bulbar poliomyelitis until additional experience has been obtained, according to the authors, but the foregoing data are encouraging.

ALPERS, Philadelphia. [A. M. A. ARCH. NEUROL. & PSYCHIAT.].

EVALUATION OF RED CROSS GAMMA GLOBULIN AS A PROPHYLACTIC AGENT FOR POLIOMYELITIS: 1. PLAN OF CONTROLLED FIELD TESTS AND RESULTS OF 1951 PILOT STUDY IN UTAH. W. McD. HAMMON, L. L. CORIELL, and J. STOKES JR., J. A. M. A. **150**:739 (Oct. 25) 1952.

The principal purpose of the experiment described in this, and in the subsequent, paper of the series was to determine whether gamma globulin, as prepared for and furnished by the American National Red Cross for measles prophylaxis, would protect against the paralytic manifestations of poliomyelitis when administered in reasonable dosage before the onset of illness. A secondary purpose was to determine, if protection were afforded, the duration of protection in the dosage selected for the experiment. Another secondary purpose was to determine whether gamma globulin would permit or interfere with inapparent or milder types of nonparalyzing clinical infection and the subsequent development of active immunity.

Hammon and his colleagues conducted a pilot study during an epidemic in Utah in September, 1951, during which 5,767 children received injections. By a method of random selection, half the children in the study received injections of gamma globulin, and the other half, injections of a gelatin solution. No significant clinical reactions of any type were observed. There was no evidence that the inoculations led to any increase or localization of paralysis.

As anticipated, the number of cases of poliomyelitis occurring in the group receiving injections was too small to permit the authors to determine whether gamma globulin had afforded any protection.

ALPERS, Philadelphia. [A. M. A. ARCH. NEUROL. & PSYCHIAT.].

EVALUATION OF RED CROSS GAMMA GLOBULIN AS A PROPHYLACTIC AGENT FOR POLIOMYELITIS: 2. CONDUCT AND EARLY FOLLOW-UP OF 1952 TEXAS AND IOWA-NEBRASKA STUDIES. W. McD. HAMMON, L. L. CORIELL, and J. STOKES JR., J. A. M. A. **150**:750 (Oct. 25) 1952.

In July, 1952, injections of either Red Cross gamma globulin or gelatin were given to 33,137 children, of ages from 1 through 6 years, in Harris County, Texas, and 15,686 children, of ages from 2 through 11 years, in Woodbury County, Iowa, and Dakota County, Nebraska.

The epidemics selected have continued in such a manner that 85 cases have occurred already in the inoculated group, and cases continue to occur. It would appear that the number of cases developing will be large enough to give highly significant findings.

ALPERS, Philadelphia. [A. M. A. ARCH. NEUROL. & PSYCHIAT.].

EVALUATION OF RED CROSS GAMMA GLOBULIN AS A PROPHYLACTIC AGENT FOR POLIOMYELITIS: 3. PRELIMINARY REPORT OF RESULTS BASED ON CLINICAL DIAGNOSIS. W. McD. HAMMON, L. L. COREILL, P. F. WEHRLE, and others, J. A. M. A. **150**:757 (Oct. 25) 1952.

In the preceding series of three controlled field tests to evaluate the prophylactic effect of Red Cross gamma globulin in poliomyelitis, 54,772 children, between the ages of 1 and 11 years, were inoculated, one-half of them with gamma globulin and one-half with a solution of gelatin. These three field tests were conducted in areas that were experiencing severe epidemics of poliomyelitis. The injections were given to apparently normal, healthy children living in the area, with the full understanding, permission, and cooperation of the parents. Which of the two materials any one child had received was unknown to all—children, parents, and investigators—until completion of a follow-up period considered to be adequate for determining a final diagnosis.

A preliminary tabulation of results as of Oct. 1, 1952, shows that paralytic poliomyelitis had been diagnosed in 90 cases in the study group. Analysis of these patients on the basis of the type of injection received shows that significant protection was conferred by the gamma globulin. During the first week after injection there was no significant reduction in the number of cases in the group receiving gamma globulin, but the severity of paralysis appears to have been modified. From the second through the fifth week highly significant protection was demonstrated. After the fifth week this was less evident, but more definite conclusions regarding the duration of protection and possible modification of the disease will be available after a longer follow-up period. Laboratory studies, still incomplete, should give information regarding the effect of gamma globulin on inapparent injection and the subsequent development of active immunity.

ALPERS, Philadelphia. [A. M. A. ARCH. NEUROL. & PSYCHIAT.].

CORTISONE AND CORTICOTROPIN IN RHEUMATIC FEVER AND JUVENILE RHEUMATOID ARTHRITIS. JOSEPH J. BUNIM, ANN G. KUTTNER, JANET S. BALDWIN, and CURRIER McEWEN, J.A.M.A. **150**:1273 (Nov. 29) 1952.

Cortisone and corticotropin therapy produces prompt clinical improvement in the extracardiac manifestations of acute rheumatic fever. It is difficult to evaluate its effect in the cardiac manifestations. Pericarditis, congestive heart failure, abnormal heart rates and rhythms are improved, but rarely is an enlarged heart restored to normal size.

Likewise, cortisone and corticotropin therapy suppresses the symptoms of juvenile rheumatoid arthritis, but, in adults, relapses occur when medication is discontinued. Adrenal cortex hormone therapy is indicated in the rheumatic state whenever the patient is threatened with invalidism or death.

KIMBALL, Evanston, Ill.

STUDIES IN HUMAN SUBJECTS ON ACTIVE IMMUNIZATION AGAINST POLIOMYELTIS. JONAS E. SALK, J. A. M. A. **151**:1081 (March 28) 1953.

Neutralizing antibodies were demonstrated in human subjects two years after they had acquired their infection naturally. Of two differently prepared vaccines, each produced appropriate and equal neutralizing antibodies four months after intradermal injection in human volunteers. Long experiments of testing for safety must coincide with the production of each new batch of vaccine before a useful vaccine will be available.

KIMBALL, Evanston, Ill.

FOUR FATAL CASES OF BULBAR POLIOMYELITIS IN ONE FAMILY. MAX J. FOX, and JOHN CHAMBERLAIN, J.A.M.A. **151**:1099 (March 28) 1953.

Four of eight children (two were not at home) contracted bulbar poliomyelitis within less than seven days of each other. All four died. All children showed petechial hemorrhages in the

dentate nucleus, the floor of the fourth ventricle, the pons, the medulla, and the anterior horns of the spinal cord. All the monkeys inoculated became paralyzed or died. The past histories of illnesses, including the number of months of breast feeding, were not reported.

KIMBALL, Evanston, Ill.

RABIES—THE DOCTOR'S DILEMMA. HOWARD J. SHAUGHNESSY, Illinois M. J. **103**:82 (Feb.) 1953.

Illinois falls in the area in which the incidence of animal rabies in very high. Since it is not always possible to determine with certainty the true risk of exposure, in practice the dilemma resolves itself into the necessity of weighing the relative risks of contracting rabies versus development of postrabic vaccine paralysis.

It may be necessary in some cases to begin antirabic vaccination of the patient before the condition of the biting animal is known. Treatment may be discontinued in a week if the animal has shown no signs of rabies in the interim. Shaughnessy reports that in a recent analysis of 25,000 cases there was an incidence of 1:1700 of postvaccinal reactions of the neuroparalytic type. Vaccination should be discontinued as soon as early signs or symptoms of impending serious reactions appear. The author also advises that reimmunization should not be given to borderline exposures and, if given, should be limited to a short booster course of five to seven injections. In Illinois, rabies rarely occurs in a vaccinated subject.

Recent studies indicate that swabbing wounds artificially contaminated with rabies virus with 1% refined benzalkonium (Zephiran) chloride is even more effective than irrigation with soap solution.

BARBOUR, Peoria, Ill.

MEASLES ENCEPHALITIS. GERALD SOLOMONS, CHARLES A. MARKMAN, and EDWARD J. WEST, Pediatrics **11**:473 (May) 1953.

Thirty-five cases of measles encephalitis over a 15-year period are reviewed. The rising incidence of this complication is suggested. The older average age and the mortality rate occurring in females is noted, and a concept based on previous central nervous system involvement to account for this is presented. The use of gamma globulin is discussed.

FROM THE AUTHORS' SUMMARY.

STUDIES ON POLIOMYELITIS IN ONTARIO: VI. ADDITIONAL LABORATORY STUDIES ON CASES OF CLINICAL POLIOMYELITIS EXCRETING COXSACKIE VIRUS. A. J. RHODES, EINA M. CLARK, W. WOOD, F. T. SHIMADA, N. SILVERTHORNE, J. B. J. MCKENDRY, DARLINE DUNCAN, and C. S. ANGLIN, Canad. M. A. J. **68**:438 (May) 1953.

Tests for homologous Coxsackie neutralizing antibody have been carried out with the sera of eight poliomyelitis patients excreting Coxsackie virus. Results suggest that in six of these the virus actually caused an infection. Two of these patients were paralytic, and in these poliomyelitis virus was also found. No poliomyelitis virus was found in the other four who were not paralyzed.

The authors conclude that the Coxsackie virus may sometimes cause a lymphocytic meningitis simulating nonparalytic poliomyelitis.

MCGUIGAN, Evanston, Ill.

MUMPS MENINGOENCEPHALITIS. D. BOWERS and D. S. P. WEATHERHEAD, Canad. M. A. J. **69**:49 (July) 1953.

Nearly 25% of all cases of mumps may be expected to show signs of meningoencephalitis. More frequent spinal fluid examinations in acutely ill mumps patients may reveal many such cases. Since meningoencephalitis may occur without evidence of mumps, it should be thought of in all cases of acute virus disease of the central nervous system.

MCGUIGAN, Evanston, Ill.

DIAGNOSIS AND TREATMENT OF BULBAR POLIOMYELITIS. W. HOWLETT KELLEHER, Lancet **1**:973 (May 5) 1951.

Kelleher reviews the diagnostic features of various types of bulbar poliomyelitis and discusses the chief aspects of treatment. He follows the classification of bulbar poliomyelitis suggested by the Minnesota Poliomyelitis Research Commission in 1947, although he states that, strictly speaking, it is applicable only to poliomyelitis with a lesion in the medulla oblongata. The classification includes the cranial nerve nuclei group, the respiratory center group, the circulatory center group, and the encephalitic group.

The cranial nerve nuclei group is divided into an upper subgroup, including the nuclei of the 3d, 4th, 5th, 6th, 7th, and 8th cranial nerves, and a lower subgroup, including the rest of the cranial nerves but concerned chiefly with the nucleus of the 10th nerve. Lesions of the upper subgroup commonly included disturbances of the fifth nerve, facial nerve paralysis, and vertigo and vomiting. Ocular signs were uncommon. In many of these cases the involvement was slight, and the author states that most of the patients partially recovered in due course.

The dangers of bulbar poliomyelitis are with lesions of the lower subgroup, particularly in cases of involvement of the 10th nerve nucleus, with resultant respiratory difficulty. The chief concern is with the accumulation of secretions, owing to neural dysfunction of the pharyngolaryngeal area, where aspiration of even small quantities of secretion into the larynx may set up reflex spasm and dangerous collapse.

Lesions of the respiratory center may be commoner than is suspected and may result in irregularities of depth and rhythm of respiration. Periods of apnea may occur, and the patient may be apprehensive and restless, symptoms which have been ascribed to hypoxia.

The author personally saw no patients with lesions of the circulatory center but describes the principal clinical features as a florid, dusky-red color, cherry-red lips, and a very rapid pulse, with varying, but usually low, blood pressure.

Symptoms of encephalitis are common in poliomyelitis and include apprehension, restlessness, irritability, twitching of facial muscles, tremors, and insomnia. Although the cause of these symptoms is not certain, the author seems to favor the theory of hypoxia of nerve cells rather than direct damage by the virus, and feels that critical effects of hypoxia on important areas, such as the respiratory and vasomotor centers, cannot be ignored.

The causes of anoxia in bulbar poliomyelitis (quite apart from that resulting from lesions of the cervical portion of the cord producing paralysis of respiratory muscles, and from interference with the proper functioning of vital autonomic centers in the medulla) are entirely mechanical or local. The most important defect of all is the accumulation of secretions in the pharynx, mainly from involvement of the 10th cervical nerve. Also important is paresis or paralysis of laryngeal abductors. Reflex laryngeal spasm, through irritation by food or fluid particles when glottic protection is defective, may be more important than is generally appreciated. The not uncommon complication of pneumonia and, particularly, atelectasis will add to, or produce, hypoxia. Finally, there is the dreaded complication pulmonary edema.

The importance of recognizing the serious effects of lesions of the respiratory and cardiovascular centers in bulbar poliomyelitis is undoubted, for in a small proportion of cases it may be possible to save the patient. Recognition of the more local and mechanical defects, leading to defective oxygenation in bulbar poliomyelitis is, because of the claimed results for therapy, of much greater importance.

In reviewing treatment, the author discusses ascorbic acid and curare among the drugs used. He also considers nasal feedings but states that he fears them except in cases of the most suitable type.

The crux of the whole problem in the physical correction of the results of pharyngeal defects in bulbar poliomyelitis is how to keep the airway clear. There are at least two distinct aids: early postural drainage, assisted by aspiration, and tracheotomy. The author believes the poliomyelitis team should include an anesthetist and a laryngologist, who should be prepared to perform tracheotomy as a carefully planned measure of prevention, rather than of cure, of the dangerous sequelae of respiratory obstruction.

MADOW, Philadelphia. [A. M. A. ARCH. NEUROL. & PSYCHIAT.].

TREATMENT OF PERTUSSIS BY CHLORAMPHENICOL. M. L. AMADASI, Minerva Pediat. **4**:824 (Oct. 15) 1952.

Twenty-five children with whooping cough were given aerosol treatments of a 10% solution of chloramphenicol in propylene glycol four times daily for 6 to 12 days. The clinical results were excellent, there being a marked reduction in the number and severity of the coughing paroxysms and in the white blood cell counts.

HIGGINS, Boston.

USE OF CHLORAMPHENICOL IN MEASLES. A. DEL PRINCIPE and F. DELLA CAVA, Pediatria **60**:168 (March-April) 1952.

In an epidemic of measles in a tuberculosis preventorium, 16 of the 21 children with measles were treated with chloramphenicol. The giving of this medication in the preexanthematous stage did not prevent the appearance of the rash. The drug did shorten the course of the exanthematous stage, there being a crisis in about 24 hours, a more rapid convalescence, and no complications. The chloramphenicol did not prevent the return of the tuberculin reaction to positive.

HIGGINS, Boston.

VITAMIN K-TETANUS TOXIN COMPLEX IN THERAPY OF POLIOMYELITIS. F. MULÈ, Pediatria **60**:261 (May-June) 1952.

Some studies have indicated that the poliomyelitis virus first attacks the neural plate in the muscle fiber and then travels along the nerve to the cell nucleus in the anterior horns. In order to attack the virus before the cell is killed, vitamin K, which has an oxidation-reduction function by reason of its quinine structure, is used. In addition, tetanus toxin is used because it will follow along the nerve trunks. A quantity of 30 mg. of vitamin K and 100 units of tetanus toxin are mixed and kept at a temperature of 37 C. for 24 hours, the vitamin K detoxifying the tetanus toxin. This mixture is then ready for injection parenterally, sometimes into the paralyzed muscle.

This medication was given to 30 children with acute poliomyelitis in the early paralytic stage; 30 patients from the previous year served as controls. The results as to muscle functions are given in the following table.

	Treated Patients	Control Patients
Good recovery	20	10
Partial recovery	9	9
No recovery	1	11

Injections of tetanus toxin were made into the paralyzed muscles of three patients who were not in the acute phase; there was no change in the tone or growth of the muscles.

HIGGINS, Boston.

ENCEPHALOMYELOPATHY DURING VARIOLA VACCINATION REACTION. F. MULÈ, Pediatria **60**:330 (May-June) 1952.

On the seventh day after vaccination and at the height of the take, a 23-month-old child became quite ill and feverish. Three days later, her temperature reached 104 F., and the child had several severe convulsions. She remained drowsy, and many petechiae appeared on her skin. There were signs of increased intracranial pressure; lumbar puncture yielded a sterile fluid under pressure. Examination of washed red blood cells was made under an electron microscope and revealed the presence of intracellular virus bodies; these cells are illustrated in the article.

HIGGINS, Boston.

SCARLET FEVER TREATMENT AT HOME. LEENA LEISTI and J. WICKSTRÖM, Nord. med. **46**:1364 (Sept. 12) 1951.

The authors recommend one intramuscular injection of penicillin procaine followed by penicillin treatment by mouth for one week in the home treatment of scarlet fever. The results

are as good as those obtained in hospital treatment. The home treatment has the advantage of being much less expensive. Two hundred three patients were treated at home and 228 in the hospital.

WALLGREN, Stockholm, Sweden.

Acute Infectious Diseases

RHEUMATIC FEVER AND RHEUMATIC HEART DISEASE: INCIDENCE IN CALIFORNIA. ALFRED F. GOGGIO, California Med. **78**:280 (April) 1953.

The statistics cited in this and other published reports appear to substantiate the impression that in California rheumatic fever, although still an important public health problem which varies widely from one locality to another, is of lower incidence and perhaps of more benign character than in most other parts of the United States. It also appears that in California aortic insufficiency may be of higher relative incidence and occurs more frequently as a clinically diagnosable sequel of rheumatic fever than does classic mitral stenosis. Congenital defects of the heart account for a large proportion of the cases of organic heart disease in children and young adults in this state.

PRYOR, Redwood City, Calif.

VIRUS AS A PRIMARY PLASMACYTOGENIC AGENT IN BRAIN TISSUE. J. B. HYDE and B. CAMPBELL, J. Neuropath. & Exper. Neurol. **10**:408 (Oct.) 1951.

In human disease plasmacytosis has been related to hyperglobulinemia and hypersensitivity reactions. Experimental hypersensitivity in animals has been studied in this respect by many authors. These studies have revealed the intimate relation of induction of the generalized hypersensitivity to the rise in plasmacytes.

The experiments of Good consisted of microinjections of various antigenic substances, such as egg white and horse serum, into the brains of rabbits, some of which had previously been sensitized to the specific substance, others not. He found that the local "secondary response" to an antigen with which the animal had previously been sensitized was characterized by a rapid and intense accumulation of plasmacytes in the inflammatory exudate.

The present paper is an account of similar experiments in which living virus was used in place of ordinary antigens. The purpose of the experiment was to determine the time scale of the plasmacytosis, seen in the local lesions provoked by virus infection, induced in brain and skin for the purpose of comparing it with that induced by the simpler protein antigens.

Hyde and Campbell found that the early stages of inflammation brought about by the injection of minute quantities of infective vaccinia and herpes virus into the skin and brains of rabbits differ from the inflammatory picture produced by noninfective (control) material in severity of the inflammation in the amount of perivascular cuffing, and in the conspicuous early plasmacytosis. They review the significance of the plasma cell.

ALPERS, Philadelphia [A. M. A. ARCH. NEUROL. & PSCHIAT.].

A CLINICAL REPORT ON AMEBIASIS IN INFANTS UNDER ONE YEAR OF AGE. CHARLES GOLDENBERG, WILLIAM H. SHLAES, and SIDNEY MINTZER, J. Pediat. **40**:290 (March) 1952.

These Chicago physicians in one year collected the cases of 872 infants with diarrhea of unknown cause and in 80 (9.2%) found amebiasis.

The diagnosis depends upon repeated careful stool examinations, and proctoscopy. Treatment included iodinized bacitracin, diiodohydroxyquinoline (Diodoquin), emetine, bismuth glycalylarsanilate (Milibis), iodochlorhydroxyquin (Vioform) and chloroquine phosphate (Aralen Phosphate). Relapses were frequent.

MACDONALD, Pittsburgh.

THE TREATMENT OF PINWORM INFECTION (ENTEROBIUS VERMICULARIS) WITH EGRESSIN. R. F. GODDARD and H. W. BROWN. J. Pediat. **40**:469 (April) 1952.

Egressin is a thymol compound first synthesized in Germany. The dose for children is 1 gm. three times a day. It is effective against pinworm in approximately 40% of cases.

MACDONALD, Pittsburgh.

MUCOLYTIC ENZYME SYSTEMS: NONSPECIFIC HYALURONIDASE: INHIBITOR CONCENTRATION IN THE BLOOD SERUM OF SIBLINGS AND PARENTS OF CHILDREN WITH RHEUMATIC FEVER. F. H. ADAMS, D. GLICK, R. C. ANDERSON, and P. DWAN. J. Pediat. **41**:258 (Sept.) 1952.

It has been reported that patients with convalescent and inactive rheumatic fever regularly have subnormal serum hyaluronidase-inhibitor values. No one knows whether persons in whom rheumatic disease develops have low hyaluronidase-inhibitor levels before the onset of the disease. If susceptibility to rheumatic fever is in part due to genetic factors and susceptible persons have low hyaluronidase-inhibitor values, these low values might also be found in the sera from a significant percentage of siblings and parents of the rheumatic fever subjects. In this report dealing with 64 parents and 67 siblings of rheumatic fever subjects, 33% had values below 15% inhibition of hyaluronidase, whereas only 10% of a group of controls showed similar depression.

MACDONALD, Pittsburgh.

URINARY BILHARZIASIS ON THE WITWATERSRAND. BOTHA DE MEILLON, N. STOFFBERG, and H. I. LURIE, South African M. J. **27**:257 (March 28) 1953.

Examination of a single urine specimen in school children in the northern section of the Witwatersrand showed an incidence of bilharziasis in the 10 to 16-year group of 10% in European children and 20% in natives attending school near the Klein Jukskei River.

MCGUIGAN, Evanston, Ill.

THE FAILURE OF THE HYDRAZIDE OF ISONICOTINIC ACID TO SHOW AN ANTI-BRUCELLA ACTION IN VITRO. V. MONTAGNA, Lattante **23**:280 (May) 1952.

Isoniazid (hydrazide of isonicotinic acid) does not impede, even in high concentration, the growth in vitro of Brucella organisms. In this regard, it differs from *p*-acetylbenzaldehyde thiosemicarbazone. This finding suggests indirectly that these two drugs have dissimilar methods in their antituberculosis action.

HIGGINS, Boston.

Chronic Infectious Diseases

OCCURRENCE OF TUBERCLE BACILLI RESISTANT TO STREPTOMYCIN IN CHILDREN WITH TUBERCULOSIS. VIRGINIA N. WILKING, ROSA LEE NEMIR, EDITH M. LINCOLN, JOSEPHINE D. MARTIN, Am. Rev. Tuber. **66**:63 (July) 1952.

The occurrence or emergence of resistance to 10 γ or more of streptomycin was tested in 152 tuberculous patients, all of them under 13 years of age. Forty-six cultures, obtained from 17 patients, of the 387 cultures tested yielded organisms resistant to these concentrations. Seven cultures were obtained from five patients not previously treated with streptomycin. These 17 patients could be divided into two major groups: one in which an obvious correlation existed between the laboratory and clinical findings and the other in which a correlation could not be made. As Alexander and others have shown, the size of the inoculum was the most important single factor in determining the emergence of resistance. Only three patients showed the emergence of resistance; two of these died, and the other failed to respond to therapy.

The other 14 did well clinically, despite the occasional appearance of resistant organisms in isolated cultures. These children showed an inconstant response to streptomycin in culture but their clinical course was good.

ROYCE, Pasadena, Calif.

THE IN VIVO AND IN VITRO EFFECT OF STREPTOMYCIN ON STREPTOMYCIN-RESISTANT TUBERCLE BACILLI. WALDEMAR F. KIRCHHEIMER, and GUY P. YOUMANS, Am. Rev. Tuberc. **66**:486 (Oct.) 1952.

Previous reports have suggested that streptomycin exerts a deleterious effect on experimental animals inoculated with streptomycin-resistant organisms, even to the extent that the virulence of the organisms is enhanced. In a carefully controlled experiment it was shown that in vivo

streptomycin therapy of mice infected with highly resistant tubercle bacilli did not adversely affect the survival of the mice and that in vitro growth of these resistant organisms is not enhanced by streptomycin.

ROYCE, Pasadena, Calif.

HISTOPLASMOSIS OF THE CENTRAL NERVOUS SYSTEM. DALE M. SCHUZL, J.A.M.A. **151**:549 (Feb. 14) 1953.

Histoplasmosis in the central nervous system of a boy of 14 years and one of 2 years is described. The inflammation is most marked at the base of the brain and characterized by perivascular granulomatous reactions in the meninges and brain substance reminiscent of tuberculosis.

KIMBALL, Evanston, Ill.

PRIMARY TUBERCULOUS INOCULATION OF AN EAR LOBE: REPORT OF AN UNUSUAL CASE AND REVIEW OF THE LITERATURE. LAURA GREY MORGAN, J. Pediat. **40**:482 (April) 1952.

In an 18-month-old child a primary tuberculous lesion developed at the site of earring puncture of an ear lobe. The primary lesion ulcerated. Regional lymphadenopathy developed. Streptomycin and paraaminosalicylic acid treatment was successful.

MACDONALD, Pittsburgh.

TUBERCULOSIS MENINGITIS. O. RUZICZKA, J. Pediat. **40**:708 (June) 1952.

A total of 114 children with tuberculous meningitis were treated with streptomycin. Forty-nine (52.6%) were alive at the end of treatment. Streptomycin was given intramuscularly and intrathecally. The intramuscular dose was 40 mg. per kilogram of bodyweight per day, up to 2 gm. daily. The intrathecal dose was 2 mg. per kilogram of bodyweight per day for one week, then 1 mg. per kilogram of bodyweight per day until the cerebrospinal fluid was improved. After that the schedule was changed to every second day for several weeks.

The author stresses that treatment should be instituted as early as possible and should be continued until the cerebrospinal fluid is normal.

MACDONALD, Pittsburgh.

THIRD GENERATION SYPHILIS: REPORT OF A PROBABLE CASE. PHYLLIS M. WRIGHT and TETSUJI INOUE, Pediatrics **11**:465 (May) 1953.

A family study tracing a syphilitic infection from grandparents to mother to infant is presented. Data are presented which fulfill the rigid criteria necessary for diagnosis of a case of third-generation syphilis.

FROM THE AUTHOR'S SUMMARY.

TUBERCULOUS MENINGITIS TREATED WITH STREPTOMYCIN. S. J. M. RUSSELL and J. MACARTHUR, Brit. M. J. **1**:192 (Jan. 24) 1953.

Russell and MacArthur present a follow-up report of results 49 to 68 months following treatment with streptomycin of 33 patients with proved meningitis. At the time of the report 12 patients were alive, of whom 9 were leading normal lives and 3 were grossly disabled; the remaining 21 had died, after periods ranging from two days to five years. Spinal block occurred in nine patients, of whom seven had died, and one of the two others still has a partial block. Intracranial calcification was noted in the roentgenograms of 10 of the 13 patients who lived long enough for it to develop. Of these, six are now well, two are disabled, and two have died. The meningitis recurred in nine children, only one of whom was alive and well at the time of the report. Two others were disabled, and the rest died as a result of the relapse.

ECHOLS, New Orleans [A. M. A. ARCH. NEUROL. & PSYCHIAT.].

TREATMENT OF TUBERCULOUS MENINGITIS IN CHILDREN. U. WIDMER and I. LANZA, Minerva pediat. **4**:366 (May 15) 1952.

The authors review the experience in the treatment of the patients in 41 cases of tuberculous meningitis at a hospital in Turin between 1947 and 1950. During the first year, 9 of the 11 children under treatment died; it is now realized that in this period the streptomycin was given in inadequate dosage and for too short a period of time.

Of 30 patients treated since that time, there have been only 14 deaths. The prognosis was poorer in the children under 3 years of age. The earlier that treatment was started after the onset of symptoms, the better were the results. All of the children with a generalized miliary tuberculosis of the lungs in addition to the meningitis died.

HIGGINS, Boston.

FREQUENCY AND SIGNIFICANCE OF TONSILLAR INVOLVEMENT IN PRIMARY PULMONARY TUBERCULOSIS OF CHILDREN. C. ZUNIN, Minerva pediat. **4**:875 (Oct. 31) 1952.

Fifty children with primary pulmonary tuberculosis were operated upon for chronically diseased tonsils. Twenty-five of the children had active pulmonary tuberculosis as shown by the blood sedimentation rate; 10 of them showed tuberculous lesions in the tonsillar tissue. Of the 25 with a quiescent or latent tuberculosis, only 1 had tuberculous tonsillar lesions. The incidence of the tonsillar involvement is ascribed to a hematogenous spread of the infection.

HIGGINS, Boston.

APPEARANCE OF LOCALIZED TUBERCULOUS FOCI AND OF TUBERCULOUS MENINGITIS AFTER PROLONGED TREATMENT OF MILIARY TUBERCULOSIS OF THE LUNGS BY STREPTOMYCIN. A. SCHIAVINI and A. PARONZINI, Minerva pediat. **4**:1071 (Dec. 31) 1952.

Of 26 cases of uncomplicated miliary tuberculosis of the lungs treated by streptomycin during the years 1948-1951 in Novara, there was only one death. Of 22 cases where the miliary tuberculosis was complicated by meningitis, there were 14 deaths; the deaths were mostly in adults and in infants under two years of age. The routine of treatment is outlined, and also 11 cases are reported where complications have ensued.

HIGGINS, Boston.

ALLERGY TO HUMAN AND BOVINE TUBERCULIN IN CHILDREN. P. REPETTO, Minerva Pediat. **5**:137 (March 15) 1953.

Routine intradermal tuberculin tests with human tuberculin (1:100) were done at a Milan hospital; there were 138 (20.3%) positive reactions. Subsequently similar tests were made on another group of children, receiving human tuberculin on one forearm and bovine tuberculin on the other forearm. Of the 247 children in this group 135 (54.6%) showed negative reactions to both tuberculins, 75 (30.4%) positive reactions to both tuberculins, 36 (14.5%) positive reactions only to the bovine tuberculin, and 1 (0.4%) positive a reaction only to the human tuberculin. Each of the children is listed according to sex, diagnosis, and whether they drank cow's milk.

The conclusion was reached that, although the type of infecting tubercle bacilli could not be proved with any degree of certainty merely because the patient reacted to one or the other tuberculin, it was apparent in this study that the bovine type of tuberculin had proved to be the more sensitive for testing and that its use could furnish additional data in the routine size-up of well children and in the diagnosis of sick children.

HIGGINS, Boston.

ELECTROCARDIOGAPHIC REPORTS ON TUBERCULOUS AND NORMAL CHILDREN UNDERGOING TREATMENT WITH ISONIAZID. A. PACI, Minerva pediat. **5**:154 (March 15) 1953.

Izoniazid was given to 28 children with active tuberculosis or with positive Pirquet tests but with active lesions. The drug did not affect the excitability of the heart or its conduction mechanism. Some modification of the T wave and of the QRS electric axis was observed.

HIGGINS, Boston.

EXUDATIVE ALLERGIC TUBERCULOUS PROCESSES IN INFANTS. M. SAGGESE and B. CROCCO, Pediatria **61**:174 (March) 1953.

The clinical and roentgenological findings in the cases of 10 infants, under 1 year of age and with primary tuberculosis, are presented, with special attention being paid to the allergic and exudative manifestations, such as enlargement of the liver and the spleen, increase in the spinal fluid pressure, and pulmonary congestion and plural edema. These manifestations would seem to contribute favorably to the ability of children to recover from primary tuberculosis.

HIGGINS, Boston.

USE OF ISONIAZID IN THE TREATMENT OF TUBERCULOUS LYMPHADENITIS. G. COCOZZA and R. FEROLA, Pediatria **61**:216 (March) 1953.

Fifteen children with tuberculous lymphadenitis were treated with isoniazid given by mouth. If there was ulceration or suppuration, the drug was also given locally. The clinical results of this therapy were very satisfactory, with sclerosis of the nodes and healing of the ulcerations within a few weeks. The tuberculin tests became more markedly positive as the healing progressed; it is suggested that this increased allergy may have been due to gradual lysis of the tubercle bacilli. The general condition of the child improved at the time that the glands were diminishing in size. Intolerance to the drug was noticed in only a few cases, and then after the medication had been given for many days.

HIGGINS, Boston.

THE MODIFICATION OF THE TUBERCULIN REACTION INDUCED BY CORTISONE. ROANO ROSSI and GIORGIO BARTOLOZZI, Riv. clin. pediat. **50**:433 (July) 1952.

The authors have examined, in 89 children, cortisone local action on intradermoreaction with tuberculin using old tuberculin and diagnostic anatuberculin in various concentrations. It was observed that while with higher dilutions (1:10,000 for old tuberculin and 1:100,000 and 1:50,000 of anatuberculin) a sharp inhibition of the reaction to tuberculin was obtained; such inhibition gradually diminished and finally disappeared completely with higher concentrations (1:1,000 and 1:500 of anatuberculin). The authors give various hypotheses to explain this phenomenon.

FROM THE AUTHOR'S SUMMARY.

THE EVOLUTION OF EXPERIMENTAL TUBERCULOSIS IN RABBITS TREATED WITH CORTISONE, WITH STREPTOMYCIN, AND WITH CORTISONE AND SREPTOMYCIN IN ASSOCIATION. F. RAGAZZINI, Riv. clin. pediat. **50**:451 (July) 1952.

The author has done experimental research on the evolution of tuberculosis in guinea pigs given cortisone acetate, streptomycin, and cortisone acetate-streptomycin treatment respectively.

The treatments in the different groups were initiated at different times after inoculation—at the same time, after one week, or after three weeks.

On the basis of the course of the experiment and the autopsy and histological findings, the author is enabled to report the following phenomena: Cortisone treatment did not modify experimental tuberculosis in guinea pigs in any substantial way; associated cortisone acetate and streptomycin treatment gave on the whole better results than simple streptomycin treatment. The antibiotic would seem to be activated more easily and more efficaciously in association with the hormone. Considering the different results obtained by other researchers, the author suggests the hypothesis that cortisone acetate exercises a varying influence on the evolution of experimental tuberculosis according to the dose, the length of time of treatment, and the time when the treatment is initiated.

FROM THE AUTHOR'S SUMMARY.

ANTIBIOTIC TREATMENT OF OSTEOARTICULAR TUBERCULOSIS WITH STREPTOMYCIN AND VIOMYCIN INTRA-ARTERIALLY. A. RIGHINI, Riv. clin. pediat. **50**:481 (July) 1952.

Five cases of osteoarticular tuberculosis were treated with antibiotic therapy with streptomycin and viomycin by the endoarterial route. The technique and the doses are described. Attention is called to the possible use of these antibiotics in endoarterial therapy.

FROM THE AUTHOR'S SUMMARY.

THE EYEGROUND IN TUBERCULOUS MENINGITIS. K. LOBR, Med. Klin. **47**:1389 (Oct. 17) 1952.

The eyegrounds of 72 children with tuberculous meningitis were examined at intervals. In the acute stage, swelling and pressure signs of the papilla predominated. The fresh foci seen in the retina were of little diagnostic value, taking into consideration the other signs and symptoms. Of 16 children with such foci, 12 also presented a miliary tuberculosis of the lungs. In more chronic cases, the changes in the arteries of the eyeground were more prominent. Lobr discusses their nature and genesis. Together with edema of the brain, papilledema was observed, which may be falsely taken as a sign of an acute recurrence.

As a consequence of insufficient circulation due to vascular changes, optic atrophy can occur. Eyeground changes may indicate a poor prognosis sooner than the clinical course.

AMBERG, Rochester, Minn.

PATHOLOGIC ANATOMY OF TOXOPLASMOSIS, F. WAHLGREN, Nord. med. **45**:349 (March 5) 1951.

The author presents a review of the morphological changes in toxoplasmosis. The findings in the lymph nodes in four adult patients with acquired toxoplasmosis are of interest and showed pure subacute lymphadenitis with swelling of the reticular cells and accumulation of the eosinophile leucocytes and plasma cells in the tissue. This pattern might possibly be of a certain diagnostic value.

WALLGREN, Stockholm, Sweden.

Diseases of Blood, Heart and Blood Vessels, and Spleen

BONE MARROW ASPIRATION: THE POSTERIOR ILIAC CREST; AN ADDITIONAL SAFE SITE. HOWARD R. BIERMAN, California Med. **77**:138 (Aug.) 1952.

The posterior iliac crest is a readily accessible site for bone marrow aspiration which is safe, is psychologically less traumatic than others, and affords representative samples of bone marrow similar to those obtained from the sternum, the vertebral spine, and the anterior iliac crest.

PRYOR, Redwood City, Calif.

CORTICOTROPIN AND CORTISONE IN BLOOD DISEASES IN CHILDREN. J. M. STICKNEY and STEPHEN D. MILLS, J. A. M. A. **150**:1279 (Nov. 29) 1952.

Single or multiple remissions in lymphatic leukemia are induced by cortisone or corticotropin in 20 to 75% of cases; however, the number of patients surviving more than one year is not high. The remissions with folic acid antagonists are longer lasting.

Cortisone or corticotropin is helpful in cases of thrombocytopenic purpura and acute and chronic hemolytic anemia, but for the latter neither is as good as splenectomy.

KIMBALL, Evanston, Ill.

SURGICAL CLOSURE OF INTERAURICULAR SEPTAL DEFECTS. HENRY SWAN, J. A. M. A. **151**:793 (March 7) 1953.

Swan reports a method of closing an interauricular septal defect by suturing a polyethylene button into the aperture. Five patients were operated on; one died postoperatively, two were improved after two years, and the other two were operated on too recently to determine the benefits.

KIMBALL, Evanston, Ill.

SURGICAL CLOSURE OF INTERAURICULAR SEPTAL DEFECTS. ROBERT E. GROSS, J. A. M. A. **151**:795 (March 7) 1953.

Direct surgical closure of interauricular septal defects were effected by operating through a rubber well sewn to the atrial wall. The blood rises to 5 to 10 cm. in the well. Working in this well, the surgeon can close the interauricular septal defect deliberately in any manner appropriate.

KIMBALL, Evanston, Ill.

DIAGNOSIS OF CONGENITAL CARDIOVASCULAR NON-CYANOTIC GROUP. STANLEY GIBSON, Illinois M. J. **101**:15 (Jan.) 1952.

Gibson discusses the signs and symptoms in cases of congenital cardiac lesions in which cyanosis is absent and in which surgery is able to relieve the condition. The conditions discussed are patent ductus arteriosus, coarctation of the aorta, and anomalies of the aortic arch.

BARBOUR, Peoria, Ill.

SURGICAL ASPECTS OF NON-CYANOTIC CONGENITAL HEART DISEASE. WILLIS J. POTTS, Illinois M. J. **101**:18 (Jan.) 1952.

Potts points out that in the field of intrathoracic surgery adequate and effective anesthesia is a necessity. In this paper he discusses the problems involved and the surgical treatment of the non-cyanotic congenital heart diseases, patent ductus arteriosus, coarctation of the aorta, and developmental anomalies of the aortic arch and its branches. BARBOUR, Peoria, Ill.

DIRECT SURGICAL ATTACK ON PULMONARY STENOSIS IN THE TETRALOGY OF FALLOT. DANIEL F. DOWNING, CARL C. FISCHER, CHARLES P. BAILEY, ROBERT P. GLOVER, and T. J. E. O'NEILL, J. Pediat. **39**:645 (Dec.) 1951.

In the approach recommended by the authors if stenosis is valvular, a suitable knife is inserted and the valve incised. If infundibular, the channel is increased in size by dilation with the finger or sound, or the obstructing tissue is removed with suitable instrument. The authors report 30 patients treated this way with an over-all mortality rate of 23.3% and an operative mortality rate of 20%. Objections to this type of operation are reviewed and advantages summarized.

MACDONALD, Pittsburgh.

TREATMENT OF ACUTE LEUKEMIA IN CHILDREN. S. LEIKIN, E. C. RICE, D. F. DELL JR., and R. J. WATERS, J. Pediat. **41**:40 (July) 1952.

Children with acute leukemia treated with folic acid antagonists live longer if therapy is supplemented with corticotropin (ACTH) and/or cortisone. MACDONALD, Pittsburgh.

ENDOCARDIAL FIBROELASTOSIS: CASE REPORTS WITH SPECIAL EMPHASIS ON THE CLINICAL FINDINGS. FORREST R. ADAMS and BENJAMIN KATZ, J. Pediat. **41**:141 (Aug.) 1952.

Endocardial fibroelastosis occurs primarily in infancy and early childhood. Although this disorder may cause sudden death of infants and children, some patients may survive for months and even years. It is likely that some patients regain enough cardiac reserve to go on and live a fairly normal life even though the heart remains enlarged. Adams and Katz believe that the diagnosis of this disorder may be suspected on clinical grounds. The major symptoms are those related to left heart failure, possibly precipitated and accompanied by respiratory disease. These are dyspnea, cyanosis, listlessness, and vomiting. Physical examination may show an acutely or chronically ill infant with fever, dyspnea, cyanosis, rales in the lungs, cardiomegaly, and possibly hepatomegaly but usually no peripheral edema. A mitral or aortic murmur may or may not be heard, depending on how severely the valves are involved. The electrocardiogram may reveal a normal or left axis deviation on the standard leads, but unipolar precordial leads usually show evidence of marked ventricular hypertrophy. In addition, there may be low negative or diphasic T waves, depressed S-T segments, and normal or increased amplitude of QRS voltage. X-ray usually shows enlargement of the heart primarily of the left side, with little or no evidence of a left-to-right shunt.

The authors have used antibotics to prevent respiratory disease and digitalis when indicated. They reject the idea that this is a collagen disease because it rarely involves the myocardium, there is usually no microscopic evidence of myocarditis, and acute phase proteins are not elevated. Elastic fibers are occasionally present in the heart valves of patients with endocardial fibroelastosis and these have not been observed in the patients with collagen disease.

MACDONALD, Pittsburgh.

COARCTATION OF THE AORTA AT THE LEVEL OF THE DIAPHRAGM TREATED SUCCESSFULLY WITH A PRESERVED HUMAN BLOOD VESSEL GRAFT. E. J. BEATTIE JR., F. N. COOKE, JOHN S. PAUL, and J. A. ORBISON, J. Thoracic Surg. **21**:506 (May) 1951.

The authors report a case of a 19-year-old woman with a coarctation of the aorta at the level of the diaphragm. An arterial segment, 7 cm. in length and 14 mm. in external diameter, was obtained from a 40-year-old man who had died of trauma 23 days previously. This segment of iliac artery was preserved in modified Tyrode solution at 4 C. This arterial segment was used

to bridge the aortic defect. The postoperative course was uneventful. This is the eighth case to be reported of coarctation of the thoracic aorta at the level of the diaphragm, and the first such case successfully treated with a preserved arterial homograft.

MEYER, Chicago.

COARCTATION OF THE THORACIC AORTA: SIGNS DEMONSTRABLE BY CONVENTIONAL ROENTGENOGRAPHY. LAURENCE L. ROBBINS and STANLEY M. WYMAN, New England J. Med. **248**:747 (April 30) 1953.

Twenty-two male patients and 9 female patients with coarctation of the aorta make up the material that constitutes this study. They ranged in age from 4 o 62 years when first examined. In 13 cases, conventional roentgenograms were checked against angiograms.

The authors emphasize that the time-honored sign of rib notching may be absent. They list the indirect roentgenologic signs which may assist in the diagnosis. In addition, the most important feature—narrowing—may be delineated by either angiography or the use of plain films and barium in the esophagus.

The x-ray techniques are described, and the use of overexposed films, rather than high-contrast films, is mentioned.

The importance of early recognition and surgical relief of this abnormality is stressed.

WHEELOCK, Denver, Colo.

A CASE OF ENDOCARDIAL FIBRO-ELASTOSIS WITH PATENT DUCTUS ARTERIOSUS FROM ABOVE THE ARCTIC CIRCLE. MILTON O. KEPLER, Northwest Med. **51**:775 (Sept.) 1952.

The author presents a case report of an 8-week-old Indian boy who died two and one-half months after the onset of an illness characterized by bouts of cyanosis, dyspnea, vomiting, and unconsciousness. A pathological diagnosis of endocardial fibroelastosis with patent ductus arteriosus was made. A brief discussion of this condition follows.

DOCTER, Seattle.

CLINICAL DIAGNOSIS OF ENDOCARDIAL FIBROSIS: ANALYSIS OF LITERATURE WITH REPORT OF FOUR NEW CASES. EDWARD C. LAMBERT, CLARE N. SHUMWAY, and KORNEL TERPLAN, Pediatrics **11**:255 (March) 1953.

Evidence has been presented which indicates that endocardial fibrosis is a relatively common cause of death from heart disease in infancy and that a presumptive diagnosis of this condition can often be made during life. The salient features are age under one year, marked dyspnea without persistent cyanosis, absence of a loud cardiac murmur on repeated examinations, enlargement of the heart, presence of femoral pulsations, and electrocardiographic evidence of left ventricular hypertrophy in the precordial leads. The chief conditions to be considered in the differential diagnosis are aberrant coronary artery, interstitial myocarditis, and glycogen storage disease of the heart, all of which are much less frequent in the authors' autopsy data. Four cases are presented in detail. In two of these, the diagnosis was correctly made before death.

FROM THE AUTHORS' SUMMARY.

Q-T INTERVAL DURING ACTIVE AND INACTIVE RHEUMATIC FEVER. SIDNEY FINKEL and JANET S. BALDWIN, Pediatrics **9**:410 (April) 1952.

A study was made of the Q-Tc interval during 249 acute rheumatic episodes: 169 episodes of obvious rheumatic carditis, 13 cases whose only evidence for carditis was a prolonged P-R interval, 20 cases with polyarthritis, and 47 cases with chorea as the only manifestation of the rheumatic process. Analysis was also made of the Q-Tc values present during an observation period varying from one to nine years in 97 of the patients who had had a Q-Tc value higher than the average normal plus one standard deviation during the acute rheumatic process.

In 79 normal controls the average value for Q-Tc was found to be 0.418, with a standard diviation (S. D.) of 0.016. In taking the average normal value plus 2 S. D. (0.450) as the upper limit of normal, it was found that the Q-Tc exceeded this value in 69% of the acute episodes of carditis, in 38.5% of the acute episodes in the patients whose evidence for carditis was a pro-

longed P-R interval, in 50% of the patients with polyarthritis, and in 17% of the patients with chorea. Therefore, it is concluded that a majority of patients with active carditis will have a prolonged Q-Tc, which suggests that a mild degree of carditis may exist.

During the period of follow-up observation, the Q-Tc value was found to have decreased over varying periods of time to a value less than the average normal plus 1 S. D. in 70 of the 97 patients in whom the Q-Tc had exceeded this value during the acute process; in 7 patients the Q-Tc remained above the average normal plus 2 S. D.

The author's findings show that after active rheumatic fever in some patients the Q-Tc value may remain prolonged over long periods of time in the absence of any manifest clinical activity or change in the cardiac status of the patient. Therefore, it is the authors' opinion that the sole finding of a Q-Tc remaining above normal range should not be considered as indicative of persistence of active carditis.

It was found that the incidence of organic heart disease at the end of the period of observation in this group did not appear to be related to the course of the Q-Tc during the inactive follow-up period.

From the Author's Summary.

Hematologic Adjustments to Cyanotic Congenital Heart Disease. Abraham M. Rudolph, Alexander S. Nadas, and Wayne H. Borges, Pediatrics **11**:454 (May) 1953.

Several infants and children with cyanotic congenital heart disease and polycythemia, but without a corresponding increase in hemoglobin, have been encountered. The presence of a normal hemoglobin level in cyanotic children is not sufficient evidence of absence of anemia. These children responded well to iron therapy; they showed a rise of hematocrit values and produced normal red cells in excessive amounts. Clinical improvement parallelled the rise in the hematocrit reading. A rise of hematocrit values above 75% accompanied a return of symptoms, possibly due to marked increase of blood viscosity. Studies on newborn infants with congenital heart disease show an absence of the usual postnatal erythrocyte decrease in very cyanotic infants but revealed a tendency toward the development of "relative anemia" after the third or fourth month of life.

From the Authors' Summary.

Report of Three Cases of Idiopathic Familial Hyperlipemia: Use of ACTH and Cortisone. Albert L. Gaskins, Roland B. Scott, and Althea D. Kessler, Pediatrics **11**:480 (May) 1953.

Three cases of idiopathic hyperlipemia with associated sicklemia in siblings are reported. One patient was treated with corticotropin (ACTH) and one with cortisone. Neither substance had any lasting effect upon the disease.

From the Authors' Summary.

The Schönlein-Henoch Syndrome in Childhood with Particular Reference to the Occurrence of Nephritis. M. G. Philpott, Arch. Dis. Childhood **27**:480 (Oct.) 1952.

Forty cases of the Schönlein-Henoch syndrome in children have been analyzed. In 19 (47.5%) nephritis developed. Fourteen patients (35%) suffered relapses, and in 12 of these nephritis developed. Of 11 patients in whom nephritis developed, the condition is still active in 4 after one year. Only 4 patients were under the age of 2 years, including one infant of 8 months. Male patients outnumbered female in a ratio of 5:3. Throat infections preceded the disease in at least 55% of the cases.

Kelly, Milwaukee.

Electrophoretic Study of the Hemoglobin in Cooley's Anemia. F. Vecchio, Pediatria **60**:413, 1952.

Electrophoretic tests indicated that the alkali-resistant hemoglobin from patients with Cooley's anemia was similar to fetal hemoglobin and was different from the hemoglobin of patients with sickle cell anemia.

Higgins, Boston.

CUTANEOUS MANIFESTATIONS OF LEUKEMIA IN CHILDREN. A. FORTINA and S. PETROCINI, Pediatria **61**:199 (March) 1953.

Multiple bluish tumors of the skin were present in children 9 and 17 months old with leukemia. The tumors varied in size from that of a grain of rice to that of an almond. Biopsies were done, and the prevailing cells were found to be histiocytes. HIGGINS, Boston.

Diseases of Lungs, Pleura, and Mediastinum

A NEW BRONCHOGRAPHIC TECHNIQUE EMPLOYING AEROSOL ANESTHESIA. JOSEPH B. MILLER, NORMAN DINHOFFER, and WILLIAM H. CONYERS JR., Am. J. Roentgenol. **68**:229 (Aug.) 1952.

A complete and detailed account of the technique for bronchography is presented. The technique is concerned with the anesthetization of the tracheobronchial tree by means of aerosol anesthetic solutions for bronchographic purposes. This procedure has certain definite advantages for use in children. The size of the aerosol particles controls, in some measure, the degree of anesthesia, and particle size is determined by the proper concentration of detergent. The detergent used is Triton A-20 and glycerin. The procedure is said to be safer than conventional methods and is relatively simple. HODGSON, Rochester, Minn.

LOBECTOMY FOR CONGENITAL CYSTIC DISEASE OF THE LUNG. C. G. MCEACHERN, R. R. MCCOY, and J. E. ARATA, J. A. M. A. **151**:992 (March 21) 1953.

A congenital lung cyst was successfully removed from a 9-day-old infant. This is the second youngest infant so treated as far as the authors can determine. KIMBALL, Evanston, Ill.

THE INFLUENCE OF THE DOSAGE REGIMEN ON THE THERAPEUTIC EFFECTIVENESS OF PENICILLIN G IN EXPERIMENTAL LOBAR PNEUMONIA. L. H. SCHMIDT and ALICE WALLEY, J. Pharmacol. & Exper. Therap. **103**:479 (Dec.) 1951.

The authors' conclusion, in part, gives an excellent summary of their important study. "A systematic comparison has been made of the effectiveness of various dosage regimens of sodium penicillin G and procaine penicillin G against established pneumococcal lobar pneumonia in the white rat. The results of this investigation have shown that as judged both by curative action (survival rate) and control of the pneumonic lesion, the 8-hourly administration of sodium penicillin G was the most effective dosage regime. This schedule was distinctly superior to 2-, 4-, 12-, or 24-hourly treatments or single doses of sodium penicillin and was significantly more effective than the 24-hourly treatments of procaine penicillin." PILCHER, Cleveland.

TWO TYPICAL CASES OF PNEUMATOCELE IN THE COURSE OF ACUTE LUNG PATHOLOGY. L. PARENZAN, Minerva pediat. **5**:148 (March 15) 1953.

In a child of 5 years a pneumatocele developed at the base of the right lung after a staphylococcic lung abscess and empyema. A pneumatocele developed in a baby of 5 months also at the base of the right lung, while he was sick with bronchopneumonia. In both cases, the pneumatoceles were shown to be still present after a period of three to four months.

HIGGINS, Boston.

Diseases of Gastrointestinal Tract, Liver, and Peritoneum

ACUTE NONSPECIFIC MESENTERIC LYMPHADENITIS. GORDON FERGUSON, A. M. A. Arch. Surg. **65**:906 (Dec.) 1952.

Clinical features, as reported, are briefly reviewed, emphasis being placed on colicky nature of pain. The appearance of the abdomen during laparotomy is described. The author's experience with two carefully explored cases of mesenteric lymphadenitis in which he discovered small areas of ileoileal intussusception leads him to believe this is the cause of the colicky pain.

YANKAUER, Albany, N. Y.

DUPLICATION OF THE STOMACH. HAROLD F. BERG and KURT MARX, J. Pediat. **40**:334 (March) 1952.

Berg and Marx report a case of pyloric obstruction secondary to partial duplication of the stomach. Duplication of the stomach is rare.

MACDONALD, Pittsburgh.

A CASE OF PERFORATED GASTRIC ULCER MANIFESTED BY HEMATEMESIS IN AN 8-WEEK-OLD INFANT. EARL B. RUBELL, FREDERICK LEIX and ROBERT A. CLELLAND, J. Pediat. **40**:337 (March) 1952.

A 2-month-old infant had suddenly vomited bright-red liquid blood and had gone into shock. His abdomen was rigid. He was too sick to be operated on. He died 12 hours later. Autopsy showed perforated gastric ulcer.

MACDONALD, Pittsburgh.

POLYMYXIN B IN PSEUDOMONAS AND PROTEUS ENTERITIS. STUART H. WALKER, J. Pediat. **41**:176 (Aug.) 1952.

Pseudomonas and Proteus species have relatively low invasive potentials; when they do cause trouble, they are apt to be secondary invaders. As such, they may prolong diarrhea in infants with preexisting enteritis. Walker reports the successful use of polymyxin B in such cases. A side-effect is oral moniliasis.

MACDONALD, Pittsburgh.

CONGENITAL HYPERTROPHIC PYLORIC STENOSIS IN A SMALL PREMATURE INFANT. B. SCHWARTZ, L. IAMELE, and IRA M. ROSENTHAL, J. Pediat. **41**:192 (Aug.) 1952.

This premature infant weighed 4 lb. 2 oz. (1,874 gm.) at birth. At the age of one month he suddenly started to vomit. There were no visible peristaltic waves, and no pyloric tumor was palpable. Surgical exploration was performed and the pylorus was found to be hard and thickened, measuring about 1.2 cm. in diameter. The pyloric tumor was incised, and the muscle layers were spread in the usual manner. The infant made an uneventful recovery.

MACDONALD, Pittsburgh.

DUPLICATION OF THE ALIMENTARY TRACT. R. T. FOX and J. T. FOWLER JR., J. Pediat. **41**:194 (Aug.) 1952.

An infant had no gastrointestinal symptoms until he was 3 months old. Then, suddenly he began to vomit and within a few hours was prostrated. When Fox and Fowler examined him, they palpated a firm movable mass in the right abdomen. There was no distention and peristalsis was hyperactive. Rectal examination revealed no palpable mass or blood on the examining finger. At operation the abdominal mass was found to be a duplication of the ileum causing obstruction. The mass was resected and an end-to-end anastomosis was performed. The patient recovered.

MACDONALD, Pittsburgh.

MASSIVE HYDROPS OF THE GALLBLADDER PRODUCING PYLORIC OBSTRUCTION IN BOY SEVEN YEARS OF AGE. C. MARSHALL LEE JR. and GAIL S. ENGLENDER, Pediatrics **11**:449 (May) 1953.

A case of massive hydrops of the gall bladder producing pyloric obstruction in a boy 7 years of age is presented. Jaundice was not present initially but occurred as a transitory postoperative complication attributed to cholangitis and hepatitis. The merits of cholecystectomy as compared with cholecystostomy in such cases are briefly discussed.

FROM THE AUTHORS' SUMMARY.

THE ROENTGEN FINDINGS IN NEUROBLASTOMA. R. S. SHERMAN and R. LEAMING, Radiology **60**:837 (June) 1953.

Sherman and Leaming state that the diagnosis of neuroblastoma should be considered in the case of an infant or a young child with evidence of an abdominal mass, adenopathy, a tumor of the eye or the orbit, or bilateral involvement of bones. Well-developed evidences of neuro-

blastoma are pathognomonic in roentgenograms of the skull. A soft-tissue mass in the region of an adrenal gland which contains calcification and presents indistinct margins in a roentgenogram of the abdomen is also an extremely reliable sign. Of equal reliability is the presence of bilateral symmetrical areas of bone destruction, showing poorly defined borders, destruction of cortex, and periosteal reaction. These lesions have a fine, patchy internal pattern, are located oftenest in the femora and humeri, and progress rapidly. The bone lesions have a tendency to produce soft-tissue masses, and they give evidence of response to x-ray treatment. The roentgenographic diagnosis of neuroblastoma depends on the changes listed above, particularly upon combinations of these changes. Most patients with neuroblastoma present two or all of the changes described.

WEILAND, Grove City, Pa. [A. M. A. Arch. Neurol. & Psychiat.].

ENCEPHALOPATHY FOLLOWING INFANTILE GASTRO-ENTERITIS. L. CROME, Arch. Dis. Childhood **27**:468 (Oct.) 1952.

Severe and prolonged infantile gastroenteritis was followed in the present case by quadriplegia, petit mal, athetosis, blindness, and idiocy. The patient died three years later from respiratory infection. Extensive lesions were found in the central nervous system and are described. They were characterized chiefly by a focal and diffuse cell loss in the superficial layers of the cortex. Numerous areas of gliosis and demyelination were also present throughout the nervous system. It is suggested that hemoconcentration with stagnation of the cerebral circulation and the resulting anoxia might have been the main links in the chain of events leading to the production of the lesions.

KELLY, Milwaukee.

SEVERE NONHEMOLYTIC JAUNDICE OF INFANTS AND THE NEWBORN. E. SCHWARZ-TIENE, Pediatria **61**:153 (March) 1953.

Three cases of severe nonhemolytic and nonobstructive jaundice in infants with death occuring when they were about 6 months old, are described. Two of the babies were sisters, born about three years apart. The jaundice was accompanied by symptoms of progressive injury to the extrapyramidal nervous system. Hypoproteinemia with a low albumin-globulin ratio was present. It would appear that a metabolic as well as a hepatic dysfunction existed in these children.

HIGGINS, Boston.

CONGENITAL ATRESIA OF THE BILE DUCTS. C. FUSARI, Pediatria **61**:226 (March) 1953.

A fatal case of congenital atresia of the bile ducts is reported with operative and autopsy findings. Early operation is recommended in such cases, in the hope that a biliary obstruction may be found and corrected surgically.

HIGGINS, Boston.

RELAXATION OF THE DIAPHRAGM. FREDERICA CALLADO, Acta. pediat. espan. **11**:508 (May) 1953.

The author presents a case of relaxation of the diaphragm which dated from birth but was discovered when the child was 2 years old. He feels that eventration is not the proper term and because of the unknown cause also discards terms which would place the etiology on the phrenic nerve or celiac ganglion.

The coexistence of megacolon or stenosis is believed to be coincidental. Nor is increased abdominal pressure believed to be an etiological factor.

Callado discusses the symptomatology and differential diagnosis and includes several roentgengrams.

ALLEN, San Francisco.

INFANTILE INTUSSUSCEPTION: REPORT OF A CASE. W. FOCKE, Med. Klin. **47**:1025 (Aug. 1) 1952.

Focke reports an intussusception in an 11-months-old boy. During the operation, about 46 hours after onset of symptoms, it was possible to reduce the invagination successfully.

AMBERG, Rochester, Minn.

Nervous Diseases

INTRANASAL ENCEPHALOMENINGOCELE. W. B. FINERMAN and EMERY I. PICK, Ann. Otol. Rhin. & Laryng. **62**:114 (March) 1953.

Finerman and Pick report the removal of an intranasal encephalomeningocele by lateral rhinotomy in an infant of 2 weeks. The tumor was found projecting through a dehiscence in the cribriform plate. The pedicle of the lesion was ligated, and a flap of septal mucous membrane was used to cover the cribriform opening. Uneventful recovery followed.

In this instance a preoperative biopsy gave evidence of the origin of the lesion in the central nervous system. The literature contains reports of 49 cases with a survival rate of only 50% following treatment, failure usually being due to an unawareness on the part of the operator that the intranasal lesion was anything but a benign polyp.

Criteria for differential diagnosis in intranasal encephalomeningocele are (1) a nasal tumor found at birth or symptoms of nasal obstruction found in early childhood; (2) a widened nasal root and an unusually large interpupillary distance; (3) external encephalomeningocele occurring simultaneously; (4) a tumor high in the nose, over which the septal mucous membrane appears to continue; (5) signs of cranial cavity communication, such as fluctuation synchronous with pulse and respiration, and (6) postoperative cerebrospinal rhinorrhea.

Since x-rays offer little diagnostic aid and diagnostic puncture and biopsy are dangerous, the best aid in diagnosis seems to be the suspicion that such an anomalous lesion might be present.

STEELE, Kansas City, Kan. [A. M. A. Arch. Otolaryng.].

INFECTIONS AND THE SUBDURAL SPACE. MARGARET H. D. SMITH, Bull. Tulane M. Fac. **12**:105 (May) 1953.

Infections may lead to subdural empyema, effusion or hemorrhage. Pathogenesis of these conditions is considered. These complications occur with sufficient frequency that the physician should be alert to the possibility of their occurence.

McGUIGAN, Evanston, Ill.

TREATMENT OF HEMOPHILUS INFLUENZAE MENINGITIS WITH CHLORAMPHENICOL AND OTHER ANTIBIOTICS. F. R. McCRUMB JR., H. E. HALL, J. IMBURG, A. MERIDETH, R. HELMHOLD, J. BASORA Y DEFILLO, and T. E. WOODWARD, J. A. M. A. **145**:469 (Feb. 17) 1951.

McCrumb and his co-workers describe their laboratory findings with chloramphenicol, chlortetracycline (aureomycin), streptomycin, and oxytetracycline (Terramycin) in experimental Hemophilus influenzae infections in mice. They found that chloramphenicol exerts significant effects in vitro and in vivo against H. influenzae. The experimental results obtained with chlortetracycline and streptomycin were slightly better. Oxytetracycline, likewise, was found to show similar protection in mice.

Twelve children with H. influenzae meningitis, of ages from 5 months to 5 years, were successfully treated with chloramphenicol. The average duration of fever after institution of therapy was 2.3 days. There was rapid improvement of the clinical condition, with return of the sensorium in 1.3 days. There were no fatalities. One of the 12 patients had neurologic residuals, but treatment of this patient was not instituted until the seventh day of the disease.

Chloramphenicol was administered by the oral and rectal routes. The mean duration of treatment of the 12 patients was 8.0 days, and the amount of antibiotic administered was 10.4 gm. Chloramphenicol treatment presented no real problem from the point of view of administration. Five patients received the antibiotic by gavage. The concentration of chloramphenicol in the spinal fluid of five patients averaged 13.2 γ per cubic centimeter, which was roughly one-half the blood level. Toxic manifestations referable to hematologic and renal functions were not observed.

The data obtained on these 12 patients invite further evaluation of chloramphenicol in the treatment of this virulent form of meningitis. Chloramphenicol lends itself aptly to clinical testing because of the relative ease of administration, lack of toxicity, and stability of the compound, making bioassay in various tissues a relatively simple procedure.

ALPERS, Philadelphia [A. M. A. Arch. Neurol. & Psychiat.].

SUBDURAL EFFUSIONS IN PURULENT MENINGITIS. H. EVERLEY JONES, Lancet **1**:891 (May 3) 1952.

Jones reports on 6 infants with subdural collections of fluid from a total of 12 with purulent meningitis treated over a nine-month period. From three of the six infants the Meningococcus was recovered; from one, Hemophilus influenzae, and in two no organism was found.

In most patients the subdural fluid is found during the first 14 days of life, but may be found up to the age of 62 days. A continued fever associated with restless anxiety and tense fontanels after three to four days of adequate therapy is an indication for needling the subdural space. The amount of fluid obtained ranges from a few drops to over 50 cc. at a time and the accumulation may be found on one or both sides. The fluid is nearly always yellow, and the protein content in the early stages is considerably higher than that of cerebrospinal fluid withdrawn at the same time. Usually the subdural space can be emptied after two or three taps, but if fluid persists after repeated taps over a period of weeks, operation for possible dissection of an underlying membrane, as in the case of subdural hematoma, may be required. Recovery is usually rapid and uneventful.

Although the cause of these effusions is unknown, the author speculates that in meningitis the arachnoid is damaged and allows the passage of a fluid rich in protein which increases in volume by osmosis.

MADOW, Philadelphia [A. M. A. Arch. Neurol. & Psychiat.].

THE STUDY OF THE CIRCULATION OF THE CEREBROSPINAL FLUID BY MEANS OF PARAAMINOBENZALDEHYDETHIOSEMICARBAZONE: A NEW DIFFUSION INDEX. R. BULGARELLI and F. M. CHIOSSI, Lattante **23**:449 (Aug.) 1952.

Fifteen to 40 mg. of paraaminobenzaldehyde-thiosemicarbazone was dissolved in 1 to 2 cc. of water and injected intrathecally by lumbar puncture; eight hours later, 2 cc. samples of spinal fluid were obtained by suboccipital and lumbar punctures, and the paraaminobenzaldehyde-thiosemicarbazone content of each was determined colorimetrically. In normal persons the amount of the drug in each sample was generally the same, the index of diffusion, $\frac{\text{mg. 100 cc. in suboccipital fluid}}{\text{mg. 100 cc. in lumbar fluid}}$, being between 0.8 and 1.0. The index of diffusion in meningitis patients (1) when there was no lumbar block was between 0.8 and 0.9; (2) when there was total or almost total spinal block, 0 to 0.2; (3) when there was a partial spinal block, 0.4 to 0.6, and (4) when there was a block limited to the base of the brain, 0.8 to 1.4. Most of the patients studied had tuberculous meningitis; with these patients it was necessary to suspend the streptomycin therapy during the course of the test.

HIGGINS, Boston.

CLINICOPATHOLOGICAL STUDIES IN EPILEPSY. OCTAVIO PEREZ VELASCO, Arq. neuropsiquiatria **8**:301 (Dec.) 1950.

Eighty-two patients with essential epilepsy were studied anatomically, the ages ranging from 8 to 60 years, with 80% of patients from 10 to 40 years of age. All the patients were chronic, and many of them had dementia; no correlation was noted in the anatomic findings, frequency of attacks duration of the illness, or age of the patient. In all patients there was an evident asymmetry of the brain, involving especially the rhinencephalon. The cerebellum was found to be smaller on the side of the smaller cerebral hemisphere. The thalami, temporal lobes, and white matter of the frontal lobes were all asymmetrical, these structures being smaller on the side on which the cornu ammonis was more severely sclerosed. Sclerosis of the cornu ammonis was observed in 92% of the cases, being usually more marked on one side than on the other. In the cornu ammonis there were fewer ganglion cells and gliosis was present. In other parts of the brain increase in glial tissue was not noted. The mamillary body was always smaller on the side of the smaller cerebral hemisphere. In 19% of the patients the septum pellucidum was dilated. Cirsoid aneurysms were often noted over the hemispheres in the frontoparietal region. The author believes that these changes are due to a developmental defect of the brain.

N. SAVITSKY, New York [A. M. A. Arch. Neurol. & Psychiat.].

News and Comment

ANNOUNCEMENTS

Fourth Pan-American Congress of Pediatrics.—The Fourth Pan-American Congress of Pediatrics will take place in Sao Paulo in July, 1954, under the direction of Dr. Leonel Gonzaga.

The following have been nominated by the executive board of the congress: Chairman, Dr. Eduardo Imbassahy; Vice-Chairman, Dr. Marcelo Garcia; Executive Secretary, Dr. Alvaro Aguiar. The latter will act for the Pan-American and the South American Congresses. His address is 43, Rua Anita Garibaldi ap. 701-Copacabana, Rio de Janeiro, Brazil.

Continuation Course in Pediatrics.—The University of Minnesota will present a continuation course in pediatrics for general physicians next Jan. 7 to 9, 1954, at the Center for Continuation Study. Recent advances in the management of common pediatric problems will be stressed. Care of the premature infant will be discussed, and the therapy of burns will be taken up along with many other topics of general interest. The course will be presented under the direction of Dr. Irvine McQuarrie, Professor and Head of the Department of Pediatrics at the University of Minnesota.

Lodging and meal accommodations are available at the Center for Continuation Study.

National Society for Crippled Children and Adults.—The 1953 Annual Convention of the National Society for Crippled Children and Adults will take place on Nov. 12-14, in Chicago.

Dedication of the Philip Charles Jeans Pediatric Library.—The annual postgraduate conference in pediatrics was held at the State University of Iowa, Sept. 16 and 17, in conjunction with the fall meeting of the state pediatric society. One session was devoted to a memorial program honoring Dr. Jeans. Speakers at this session were Dr. Jean V. Cooke, Professor Emeritus, Department of Pediatrics, Washington University School of Medicine, St. Louis; Dr. L. A. Maynard, Professor and Head of the School of Nutrition, Cornell University, Ithaca, and Chairman of the Food and Nutrition Board of the National Research Council; Dr. James R. Wilson, Secretary of the Council on Foods and Nutrition, American Medical Association. Particular emphasis was given to Dr. Jean's long service and many contributions as a member of national advisory boards, for this phase of his professional life was less familiar to physicians of the state.

The dedication followed the talks. Dr. Lee Forest Hill, of Des Moines, read a eulogy of Dr. Jeans. The library was then dedicated to Dr. Jeans by Dr. Charles D. May, Professor and Head of Pediatrics, State University of Iowa. The dedicatory plaque reads as follows: "This library is dedicated in appreciation of Philip Charles Jeans, M.D., Professor and Head, Department of Pediatrics 1924-1952. A wise clinician, thorough investigator, humble teacher, and understanding friend."

National Foundation for Infantile Paralysis Announces Postdoctoral Fellowships.—The National Foundation for Infantile Paralysis announces the availability of a limited number of additional postdoctoral fellowships to candidates whose interests are research and teaching in medicine and the related biological and physical sciences. The purpose of these National Foundation fellowships is to increase the number of professional workers qualified to give leadership in the solution of basic and clinical research problems, including those of poliomyelitis and other crippling diesases.

The fellowships cover a period of from one to five years. Stipends to Fellows range from $3,600 to $7,000 a year, with marital and dependency status considered in determining individual awards. Institutions which accept Fellows receive additional compensation for expenses incurred in relation to their training programs.

Eligibility requirements include United States citizenship (or the declared intention of becoming a citizen), sound health, and an M.D., Ph.D., or an equivalent degree.

Selection of candidates is made by a Fellowship Committee composed of leaders in the fields of medical research and professional education. The designation "Fellow of The National Foundation for Infantile Paralysis" will be given to successful candidates.

A total of 181 fellowship awards in these categories has been made by the National Foundation up to Aug. 1, 1953.

Complete information concerning qualifications and applications may be obtained from the Division of Professional Education, The National Foundation for Infantile Paralysis, 120 Broadway, New York 5.

Postgraduate Pediatric Refresher Week.—The theme for the annual postgraduate pediatric "refresher week" at Tulane University of Louisiana School of Medicine Feb. 8-13 this year will be "Surgery for Infants and Children." The program will be under the direction of Dr. Ralph V. Platou and Dr. Alton Ochsner, with Dr. Willis Potts and Dr. Thomas Baffes as guest speakers. Major emphasis will be given to consideration of medical and emotional preparations and after care, choice and conduct of anesthesia, diagnostic procedures, and recent advances in related fields. Those interested should apply to the Director, Division of Graduate Medicine, 1430 Tulane Ave., New Orleans 12. Registration, as usual, is limited to 40 qualified specialists.

PERSONAL

Dr. Edith Potter Awarded Honorary Degree.—Dr. Edith Potter, internationally famed pathologist of the Chicago Lying-In Hospital of the University of Chicago, was awarded an honorary degree—doctor honoris causa—by the University of Brazil at Rio de Janeiro on Oct. 1.

Award for Dr. Herbert B. Wilcox.—Dr. Herbert B. Wilcox, Professor Emeritus of Pediatrics at Columbia University, is one of 25 persons who will receive Distinguished Service Awards in connection with the 25th anniversary of Columbia-Presbyterian Medical Center on Oct. 12 and 13. The awards, first of the kind ever made by the institution, will commemorate the contributions by Dr. Wilcox and his colleagues to the growth and development of the Medical Center.

Dr. Wilcox, who graduated from Columbia University College of Physicians & Surgeons, in 1902, has a total service record of 37 years in medical science. He was associated for virtually all of this period with Columbia, having retired in 1939.

Dr. Wilcox was Medical Director of Babies Hospital, now a unit of the Presbyterian Hospital. A leader in the field of pediatrics, he has done extensive work in diabetes, child cardiac conditions, meningeal diseases, kidney function and growth, lead poisoning, and parathyroid glands. He has been a member of the White House Conference on Child Health and Protection, and also a member of the New York Commission on Crippled Children. He is a trustee of the Child Health Association, and a past director of the New York Academy of Medicine.

Appointment for Dr. Henry W. Kumm.—Dr. Henry W. Kumm of Chocorua, N. H., and New York has been appointed director of research of the National Foundation for Infantile Paralysis, it was announced by Basil O'Connor, president.

Books

Mass BCG Vaccination in Poland 1948-1949, with Special Reference to Statistics on Tuberculin Testing and BCG Vaccination. Prepared by the staff of the statistical section, Tuberculosis Research Office, World Health Organization, Copenhagen, under the direction of I-Chan Yuang, M.D., with assistance of Jørge Nyboe. Price, not given. Pp. 134, with 1 illustration, 10 charts, and 4 tables. The International Tuberculosis Campaign, Copenhagen, Denmark, 1950.

The statistical staff has done a very complete piece of work in reporting and analyzing the large amount of material collected during the BCG vaccination campaign in Poland. This is, up to the present, the most extensive program in any individual country that has participated in the international BCG campaign. Approximately 5,000,000 persons from the ages of 1 to 18 years were tuberculin tested. This number represents about 60% of the Polish population of that age group. Over 2,000,000 negative-reactors were vaccinated. The program was carried out under the joint auspices of the Polish Ministry of Health, the Danish Red Cross, the Norwegian Relief for Europe, the Swedish Red Cross, and the United Nations International Children's Emergency Fund.

The report is presented in four sections. In the first, the organization and management of the campaign is described. In the second, the variability, completeness, and reliability of the collected statistics is discussed. In the third, charts and graphs are presented, analyzing the material as to age, sex, and county of residence. The fourth section consists of the tabulated statistics.

The present value of such a report is twofold: first, as a guide to similar campaigns, and second, as an indication of the distribution and extent of tuberculous infection in Poland. Its ultimate value will be to help estimate the worth of BCG vaccination in the control of tuberculosis.

The International Tuberculosis Campaign, July 1, 1949—June 30, 1950. Second Annual Report. Price, not given. Pp. 333, with numerous illustrations. Issued by the International Tuberculosis Campaign, 25 Svanemøllevej, Copenhagen, Denmark, 1950.

This is a companion volume to a previous publication, "The Conference on European B. C. G. Programmes." It is a report of the progress made during the 12 months from July 1, 1949, to June 30, 1950, on the mass BCG vaccination program now being conducted on an international scale under the auspices of the Joint Enterprise. The organizational set-up of the Joint Enterprise under the International Tuberculosis Campaign (ITC) is reviewed, and detailed explanations are presented of many of the more important phases of the work. Thus methods of construction of a laboratory for the production of BCG are described, and copies of the literature used for collecting statistical data are reproduced. Expenditures to date are listed, and the number of units of tuberculin, BCG syringes, and other material supplied to the various countries are given. Specially constructed refrigerator containers for transport of BCG vaccine are described. These were found to be important in order to insure stability and uniformity of the vaccine at the time of its use in the field. The number and type of personnel assigned to the different countries are listed, as well as the size of the motor transport and the type of vehicles.

In addition to documentary details of the mechanics of operations, information is given on what has been learned about the most suitable kind and amount of tuberculin for prevaccination and follow-up vaccination testing. Interestingly enough, all tuberculin used in the ITC program has been standardized so that the dose can be expressed in units. Thus 100 tuberculin units corresponds to 1.0 mg. O. T. While a final decision has not yet been reached, the report indicates that a Mantoux test of 5 tuberculin units appears to give the most satisfactory results for both pretesting and follow-up testing.

A large portion of the report is devoted to the campaigns in the individual countries. During the year covered by the report, BCG campaigns were inaugurated in many countries outside

Europe. These include North Africa, the Middle East, Asia, and Ecuador and Mexico in Latin America. The statistical summary as of June 30, 1950, gives a grand total of 22,582,792 persons tested to tuberculin, of whom 8,247,541 were reactors, and 10,845,455 were vaccinated with BCG.

The final section of the report discusses plans for continuation of BCG work by United Nations agencies upon termination of the ITC. Actually ITC concluded its emergency and demonstration programs in January, 1951, when it was expected some 15,000,000 persons would have been vaccinated. However, both UNICEF and WHO will continue to assist nations in BCG work as part of the general antituberculosis program.

To the reviewer these reports by ITC are an extremely valuable contribution to the world problem of tuberculosis control. They constitute blueprints to any country desirous of undertaking a mass BCG vaccination program on its own. Finally, when the statistical data are collected and analyzed, it should be possible to have an answer to the place of BCG in the prevention of tuberculosis.

Kinderarzt und Erziehung für Ärzte, Studierende u. Erzieher. By Prof. Dr. Herbert Schönfeld. Boards. Price, 6.40 marks. Pp. 130. Ferdinand Enke, Hasenbergsteige 3, Stuttgart, W., 1951.

Though not intended as a text limited to strictly medical consumption, this small volume is full of material the German-reading pediatrician would welcome. Not that there is much that is new and spectacular; on the contrary, the discussion brings out the point of view the pediatricians of this country have held for many years. It is a practical philosophy on the emotional development of the child, the different patterns of psychologic reactions exhibited at the various age levels, and the parental responses these reactions generally evoke.

Problems in conduct and behavior are traceable to the genes at times, but more frequently to maternal feelings of incompetency and insecurity. This is brought out in early chapters on "Fehlerhafte Säuglingserziehung" and "Schwererziehbare Säuglinge." Thus the author properly differentiates between results of faulty management of the infant and the infant who is generally considered neuropathic. This distinction, unfortunately, is not too clear to the reviewer, who vainly hoped to find a convincing explanation of the unpopular syndrome (?) infantile colic, which, as we all know, is common to both types mentioned by the author.

To Schönfeld's credit, however, it is fair to state that the volume is most favorably unique in that the material covered is well arranged and much superior in a class of books generally more confusing than informative and almost universally theoretic rather than realistic. Of unusual interest is the chapter entitled "Ethische Grundfragen." To the author, the goal is not the bringing up of a "good" child, but to train the child from early infancy in the utilization of all of his potentialities for the good of society. In this chapter are discussed the various relationships of all concerned with the development of the young organism and the reversible pressures, judgments, and attitudes and their effects on the ethical standards with which the child reaches maturity.

Taken as a whole, this book offers a practical and wholesome philosophy on child development. It cannot be recommended as a reference volume on therapy in behavior disorders. However, the physician interested in this field of pediatrics will find it instructive and pleasant to read.

La talassemia (morbo di cooley e forme affini). By G. Astaldi, P. Tolentino, and C. Sacchetti. Price, 2,500 lire. Pp. 229. XII. bibliotheca haematologica, fondata da A. Ferrata, Pavia, Italy, 1951.

Although Cooley, in Detroit, first described the fundamental characteristics of erythroblastic anemia, it has been in children of Italy and Greece that almost all the cases have been observed. Where there are many cases, it is to be expected that clinical observation and research should predominate. Thus Italian pediatricians and hematologists have contributed much in the past few years to an understanding of the disease and especially of its cause. This treatise on thalassemia is Number 12 of Ferrata's series on hematology, and expresses clearly and convincingly an Italian concept of the disease. A well-expressed 12-page summary in English is included, and should be welcomed by American readers.

Thalassemia is not a new disease, fossil remains in Sicily having revealed what seem to have been cases of the disease.

The authors recognize three types of thalassemia. Thalassemia major, or Cooley's disease, is homozygotic and always fatal. Thalassemia minor, or Rietti-Greppi-Michaeli disease or anemia, is heterozygotic, mild, and not fatal. Thalassemia minima, or microcythemia of Silvestroni and Bianco, is a carrier state without symptoms. It appears that Cooley's anemia appears only if both parents, and Retti's disease only if one parent, had the hematological anomaly of thalassemia minima.

It is suggested that thalassemia is due to a spontaneous mutation occurring in an archaic race living in the Mediterrean region. Thalassemia major can be prevented if two individuals with thalassemia minima do not procreate.

The signs and symptoms, and especially the physiopathology, of the three types of thalassemia are well described. The short life span of the erythrocyte, compensated for by medullary hyperplasia, is stressed as the basis for the disease.

The book is recommended as a presentation in a clear and new manner of the basis of symptoms and signs of a disease which has been quite confusing to most of us.

Medicina infantil. Edition 7. By Juan P. Garrahan. Price, 180 Argentine pesos. Pp. 1,196, with 197 illustrations. Libreria y editorial "El Aleneo," Florida 340—Córdoba 2099, Buenos Aires, 1951.

This is a seventh edition of a textbook on pediatrics, which is the most popular in Latin America, and probably in the Spanish language. This edition is fully revised and is a compliment to the erudition of the author. A very complete and well-written textbook in Spanish.

La puericultura del lactante en España. By Juan Bosch-Marin. Price, not given. Pp. 42, with 10 graphs and 11 tables. Publicaciones al Servicio de España y del Niño Español. No. 160, Madrid, 1951.

This book gives by tables and graphic representation the strides that have been made in child care in Spain in the last 50 years. In 1901 the infant mortality was 186 per 1,000 live births. In 1950 it was 63 per 1,000. These results have been obtained by intensive control of digestive disturbances and infectious diseases. Special effort is now being made on immunization against diphtheria and pertussis, with emphasis on BCG vaccination for tuberculosis.

Memorias del servico de medicina interna Dr. Pavon. By Dr. Ramiro H. Caballero. Paper. Price, not given. Pp. 37, with 18 illustrations. Paratipos, S. A., Habana, Cuba. 1950.

This book contains five articles republished from the Medicina latina, Habana, 1943 to 1946.

CORRECTION

In the Directory of Pediatric Societies in the October, 1953, issue, page 549, the names and addresses of the President and Secretary of the Cincinnati Pediatric Society were reversed. The correct entry for this Society is

CINCINNATI PEDIATRIC SOCIETY

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Secretary: Dr. Clare R. Rittershoffer, 301 Erkenbrecher

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1. Drabkin, D. L.: Metabolism of Hemin Chromoproteins, Physiol. Rev. *31*:345 (1951).
2. The Biosynthesis of Hemoglobin, Editorials, J.A.M.A. *150*:1223 (Nov. 22) 1952.

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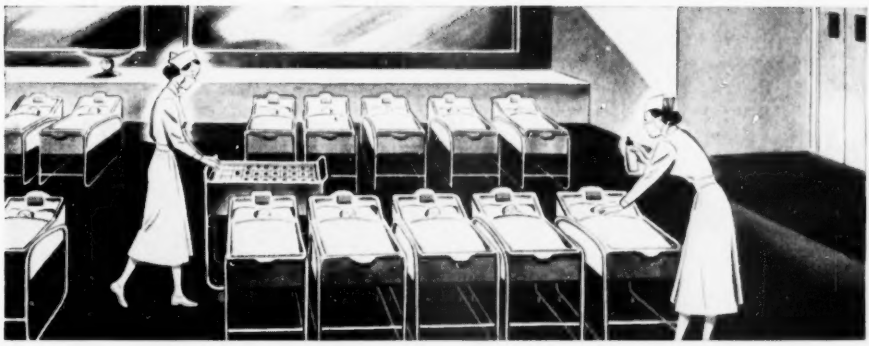

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Meyer, H. F., "Essentials of Infant Feeding for Physicians" Thomas (1952)

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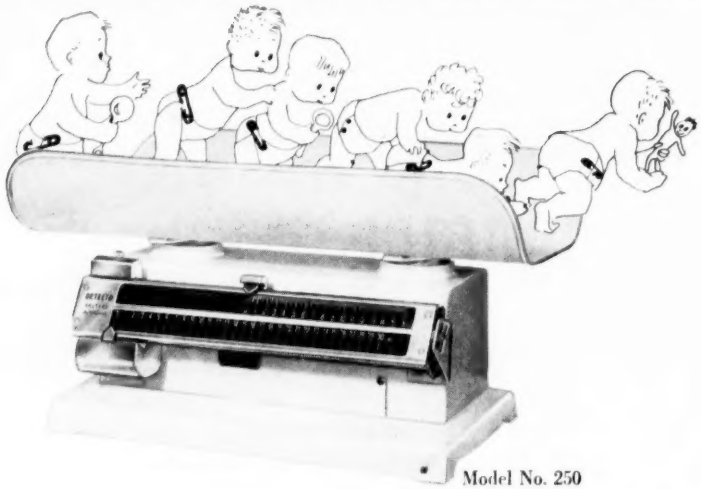

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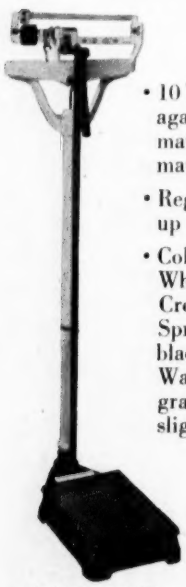

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Gunther, M., Brit. J. Nutrition 6 (No. 2): 215, 1952.

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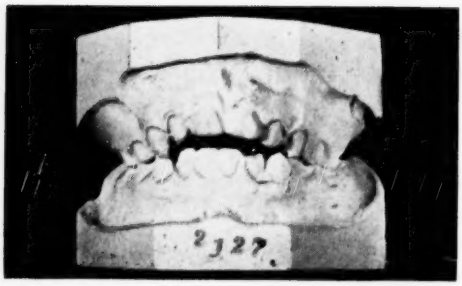

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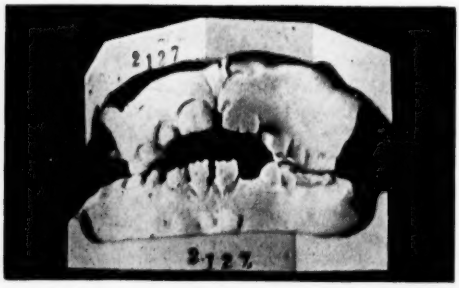

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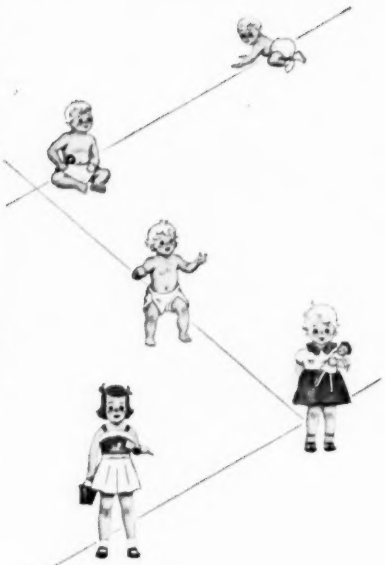

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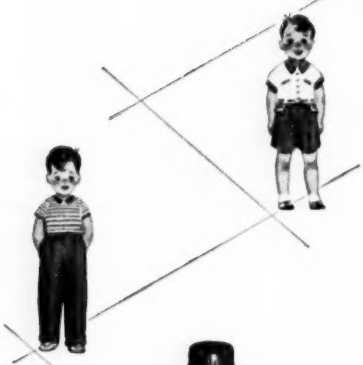

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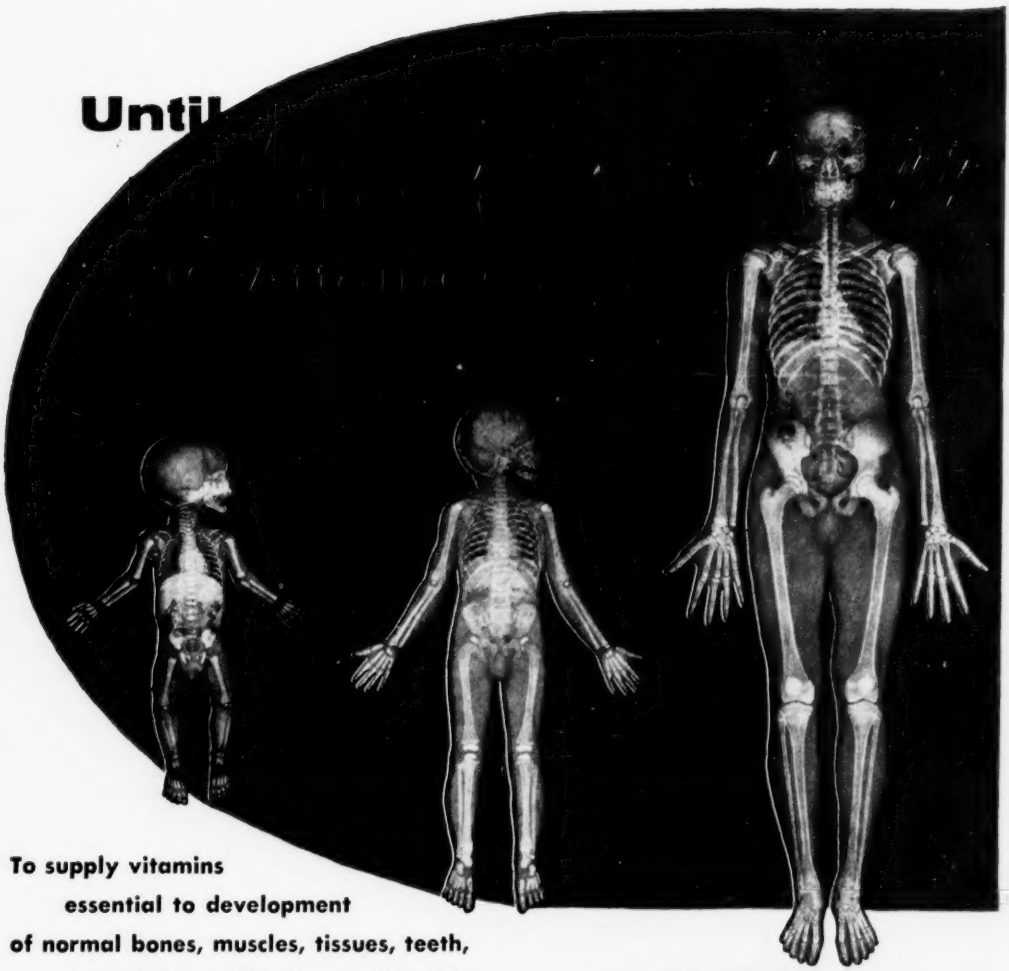

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